A MOUNT SINAI HOSPITAL MONOGRAPH ON

Systemic Lupus Erythematosus

EDITORS

GEORGE BAEHR, M.D.

and

PAUL KLEMPERER, M.D.

CONTRIBUTIONS TO THE SYMPOSIUM

BY MEMBERS OF THE STAFF OF THE MOUNT SINAI HOSPITAL, NEW YORK

BARUCH J DAVIS, M D
GABRIEL C GODMAN, M D
DONALD GRIBETZ, M D
WALTER L HENLEY, M D
SAUL JARCHO, M D
STANLEY L LEE, M D
ABOU D POLLACK, M D
LOUIS J SOFFER, M D



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PREFACE

The problem of systemic lupus erythematosus has held the interest of the medical staff of The Mount Sinai Hospital for the past thirty years; since the days when *Dr Emanuel Libman was Attending Physician to the institution*

Before Kaposi's original description of the disease in 1872 as a serious, acute, often fatal disease entity, lupus erythematosus had been regarded merely as a persistent but generally innocuous malady of the skin Dermatologists almost exclusively were concerned with its diagnosis and empirical therapy. About the turn of the century its general medical implications became evident to clinicians Various internists collaborated in attempts to define the obscure and puzzling clinical picture of the disease The manifestations of joint, kidney and serous membrane involvement were clearly described and associated hematologic alterations were discovered in the laboratory. However, specifically characteristic pathologic-anatomic and histopathologic lesions first became known through Libman and Sacks' classical paper in 1924.

Since that time numerous additional microscopic observations were made which aided in clarifying the nature of the disease. These observations of altered structure of organs and tissues focused attention upon the obscure pathogenesis of the condition The discovery of the lupus erythematosus cell by investigators at the Mayo Clinic coincided with the first cytochemical analysis of the hematoxylin stained bodies demonstrated in tissues by Dr Louis Gross in our laboratory in 1932 Subsequent morphologic studies led to the establishment of dependable diagnostic criteria of systemic lupus erythematosus, and to hypotheses regarding the chemical mechanism responsible for the structural changes in the blood and tissue cells Therapy was significantly advanced for the first time by the discovery of the corticoids More recently, the disclosure of a L E factor in the serum of patients attracted the attention of immunologists and their studies have given new leads to the elucidation of the problem of etiology.

The history of systemic lupus erythematosus illustrates the path by which progress is achieved in medicine exact observations made at the bedside and at the autopsy table led to research by means of the refined methods of fundamental biology

A survey of the present state of our scientific knowledge of systemic lupus erythematosus seems timely and we have therefore invited a number of competent investigators to cooperate in summarizing current information on the subject *All are on the staff of The Mount Sinai Hospital or have been associated* with us in the past

George Baehr, M.D
Paul Klemperer, M.D
Editors

SOME OBSERVATIONS ON THE PATHOLOGY OF SYSTEMIC LUPUS ERYTHEMATOSUS

ABOU D POLLACK, M D

Baltimore, Md

The historical development of lupus erythematosus as a systemic disease has been critically developed by Klemperer (1) In his brief review he traced the changing conception of this malady from that of a cutaneous disorder to one in which the entire organism is profoundly disturbed This is now abundantly clear It is also clear that, in any disease presenting such diverse and apparently unrelated manifestations, one must search for a catastrophe at a very basic level

It is traditional, in developing a comprehensive concept of any discrete disease, to explain the alterations in form and function on a single pathogenetic principle I am not sure that this is always the best starting point It may be more profitable to assume, or we may even be forced to assume, that the many manifestations of systemic lupus erythematosus* reflect one or more derangements, associated or not, but always interdependent One is impelled to make an acoustical analogy the total tone characteristic for a given musical instrument consists not only of a fundamental tone but also of harmonic tones heard simultaneously with and over the fundamental tone Although we have not yet identified the "fundamental tone" in systemic lupus erythematosus it is perhaps possible to sort out one or more harmonics

It is not the purpose of this paper systematically to review the many organ changes apparent in systemic lupus erythematosus The morphological manifestations have been fully documented in a number of papers (2–5) Before discussing the lesions to be found in S L E one ought to re-emphasize the disappointing (and puzzling) paucity of anatomical change occasionally found on careful post-mortem examination of a patient dying after the most fulminating and severe clinical course

The pathologic alterations in S L E seem to fall into three groups The lesions in the first group exemplify the "anatomical symptoms" of a widespread disturbance within the connective tissue system The second group of lesions reflects injury to the nuclei of cells of mesenchymal origin, especially hematic cells, and perhaps other cells as well The third group of alterations, granulomatous in character, follows from the first and second groups

THE CONNECTIVE TISSUE LESIONS

The writer and his co-authors once expressed the idea that the morbid anatomical image in S L E was a reflection of extensive damage in the connective

The Departments of Pathology, The Baltimore City Hospitals and The Johns Hopkins University School of Medicine Baltimore Md

* This recent term (and its rubric S L E) seems more appropriate than previous designations such as acute or disseminated lupus erythematosus

tissues and that the underlying functional disturbance responsible for these changes was not evident (5) They further generalized that S L E. could be considered in common with a number of other conditions (scleroderma, rheumatic fever, rheumatoid arthritis, periarteritis nodosa, thromboangitis obliterans, and serum sickness) as "collagen diseases" only in so far as all presented visible alterations in the connective tissue system, more or less similar, but each in a characteristic pattern (7). The expression "collagen disease" was devised as one of convenience, a sort of shorthand symbol to designate this group. Since its original use, the expression has been corrupted and abused to indicate disease *of* connective tissue, if indeed, there be such a thing To others the term has become synonymous with the various syndromes of hypersensitivity. To still others, "collagen disease" evokes the idea of a single nosological entity having several manifestations, e g , S L.E., rheumatoid arthritis, scleroderma, etc It is hoped that "collagen disease" will be considered in the sense of its original implication· that certain disorders, some related, some not, may have their morphologic expression in alterations of the connective tissues and that the latter comprise a system whose functions must first be defined chemically and physically before an understanding of its changes becomes possible The accelerated pursuit of basic information regarding this most important system in recent years has been most gratifying If "collagen disease" as a poor or even fallacious generalization has served no other purpose than again to call attention to the connective tissues as a functional system (8), it will have served well enough

Connective tissue consists of fibroblasts, and collagen, reticulum and elastic fibers imbedded in and continuous with a complex, amorphous "ground substance " Structural changes in the "collagen diseases" may appear in some or all of these elements in variable degree and in different quality. One of the most striking changes in S L E is so-called fibrinoid degeneration of the connective tissues These alterations are now well known and can be demonstrated in variable frequency and intensity in the connective tissue of the heart and blood vessels, kidneys, serous membranes and skin, as well as in the less organized, dispersed, connective tissues (Figs 1, 2, 3, 7).

Neumann first characterized fibrinoid degeneration as a particular kind of change in connective tissue fibres and possibly also in the ground substance· "dass eine mit Aufquellung und Homogenisierung verbundene chemische Veraenderung der Interzellularsubstanz des Bindegewebes erfolgt, welche dieselbe einer Faserstoffmasse aehnlich macht" (9) Wolpers, employing electron microscopy, would have us believe that the collagen fibre is not in itself altered but merely suffused with precipitated tissue fibrin which causes the individual fibrils to become stuck to each other (10). He stressed particularly a peculiar granular change in the surrounding amorphous ground substance. These disturbances were noted in subcutaneous rheumatic nodules and in the experimental Arthus phenomenon Rich and his co-workers, on the other hand, also having applied electron microscopy to collagen fibres from cutaneous Arthus lesions, would urge that the fibres themselves are altered, independently of any change in the surrounding ground substance (11).

Fig 1 Splenic capsule Conglomerate of pycnotic nuclei and L E bodies, both discrete and coalescent (hematoxylin bodies) interspersed with masses of fibrinoid ×165

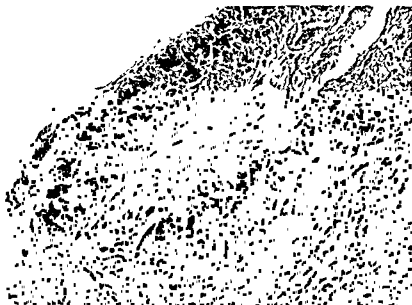


Fig 2 Splenic capsule Surface masses of fibrinoid and coalescent L E bodies (hematoxylin bodies), organization Lesion essentially like that occurring in the endocardium ×165

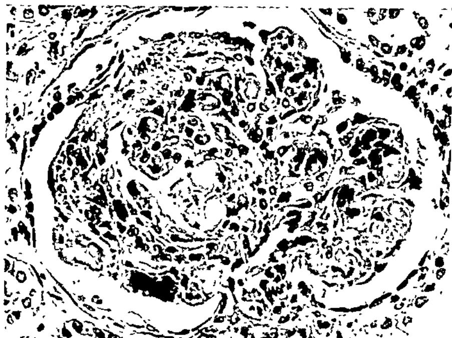


FIG 3 Kidney Fusion of endovascular and pericapillary fibrinoid masses Focal loop necrosis (left) Adhesions Discrete L E bodies in glomerular loops (upper right) Fibrinoid suffused with material of L E bodies (lower left) X350

Klemperer and Altshuler and Angevine insist that the essence of fibrinoid consists, topographically at least, in a change occurring within the connective tissue ground substance (12, 13) If we assume that collagen fibres imbedded in the ground substance form together a continuum, the difficulties inherent in assigning a particular localization of this alteration fade considerably. It is reasonable, in the face of observational and histochemical evidence, to view fibrinoid as a change occurring in the ground substance and involving the collagen fibres or not

Having accepted, for the moment, this particular localization of the fibrinoid change, how shall we regard it, of course, in the most general terms? There seem to be but two possible views In the first of these, as expounded by Klemperer, fibrinoid represents a particular localization of abnormal proteinic material in the ground substance (14) In S L E this is thought to be derived from products of degraded protein which are either precipitated locally, at the site of degradation, or transported by the blood stream, diffusing therefrom into the surrounding milieu In this way fibrinoid might be found at any depth in the vascular wall, in the pericapillary basement membrane (wire-loops of glomeruli) and even within capillary loops where local hemodynamic disturbance might lead to intravascular concentration and precipitation of circulating abnormal material In this way too has Klemperer explained the variable "histochemical appearance" of fibrinoid in S L E by assuming more or less co-precipitation of DNA with the fibrinoid complex This is, therefore, a unique kind of fibrinoid, pathognomonic

for S L E Immunohistochemical manipulation of S L E fibrinoid reveals that it contains gamma globulin (15, 16) This seems reasonable if we assume that anti-DNA or anti-nuclear immune bodies have been fixed to DNA which had previously suffused into and been precipitated in the specific S L E fibrinoid In extension of his argument, Klemperer would presume that there could be different varieties of fibrinoid, each possibly specific for a particular morbid state (and each awaiting pathogenetic characterization) (12) If this conception be broadened to include all eosinophilic, refractile, non-fibrinous material abnormally precipitated in the connective tissue ground substance then we might also include amyloid as another special kind of fibrinoid, more or less chemically discrete One is rather loath to press ratiocination in this vein and looks forward to the time when descriptive terms such as fibrinoid, amyloid, paraamyloid, and hyalin will, in the further course of experimental and chemical analysis, have become superannuated

The essence of Klemperer's conception of fibrinoid is that it represents a substance which has been added to and deposited in the connective tissue On the other hand, Altshuler and Angevine propose the second of the two possible views mentioned above, namely that fibrinoid represents a local alteration in the ground substance, and more specifically, that acid mucopolysaccharide in the presence of locally mobilized basic proteins is converted into fibrinoid

In our present state of ignorance it is not begging the question tentatively to conclude that there are indeed different kinds of fibrinoid, that the fibrinoid of S L E is quite pathognomonic in that it often contains DNA (12), and that although fibrinoid may in some states represent material brought to the ground substance and precipitated there, it may, in other states, be produced locally by physical and chemical alteration of some moiety of the ground substance

Bearing in mind these provisional tenets, it is apparent that the term fibrinoid will be used most constructively for the present in its descriptive sense only, until more pathogenetic sorting out in clearly defined terms has taken place Also, it would probably serve the cause of confusion less if we were not to identify this already complex problem with other tissue phenomena of similar appearance and even similar morphogenesis Thus, the variety of pulmonary hyaline membranes in rheumatic fever, in uremia, in paranatal primary atelectasis, in various respiratory infections —these are problems in their own right whose solution is not advanced by the loose application of the term fibrinoid, even in its descriptive sense Similarly, even should it be confirmed that intracapillary thrombi occurring in the generalized Shwarzman phenomenon do indeed represent precipitation of partially polymerized fibrin (17), the application of the term fibrinoid to these masses might inevitably suggest to some that fibrin is an essential of all fibrinoid * This is very likely not true (13) Although arbitrary, it would seem best for the moment to reserve "fibrinoid" only for the characteristic change within connective tissue, with the understanding that surface or endovascular accumulations of this group of substances may have a similar pathogenesis

* These authors imply that while fibrinoid is derived from fibrin the particular fibrinoid precipitated in their experiments contains not fibrin but a fibrin like material We have happily been spared *fibrinoidoid!*

THE CELLULAR CHANGES

It was Gross who first noted a peculiar and pathognomonic cellular alteration in the endocarditis of so-called Libman-Sacks disease (2), now recognized as one of the more striking organ changes sometimes encountered in S L E He described "hematoxylin-stained bodies" and believed them to represent "somewhat pycnotic and karyorrhectic nuclear masses." Eight years later Ginzler and Fox described similar bodies within areas of necrosis in lymph nodes and in addition, noted degenerated violaceous nuclei in the renal glomeruli of a young male with S L E (4) Klemperer, Pollack, and Baehr made reference to and illustrated peculiarly degenerated and "bizarre" nuclei occurring most frequently in association with fibrinoid degeneration of connective tissue in the heart, blood vessels, serous membranes, and glomeruli (5) None of these authors fully appreciated the full significance of these cellular changes Nor could they have

The discovery of the "L E cell" by Hargraves, Richmond, and Morton (18) marked the beginning of a new phase in the slow unravelling of the pathogenesis of S L E The immediate result of this observation was the realization of the relatively greater frequency of this disease than had been previously appreciated. Furthermore, the accelerated search for L E cells forcefully revealed the many clinical syndromes under which S L E could masquerade More important, however, has been the development of an appreciation of the relationship between "L E cells" and "hematoxylin bodies" We are indebted to Klemperer and his co-workers for noting the configurational, tinctorial, and histochemical similarity between "hematoxylin bodies" phagocytosed by histiocytes or polymorphonuclear leucocytes and the L E cells of bone-marrow aspirates (19) There now seems little doubt that these two structures reflect the same phenomenon, the one produced *in vitro*, the other occurring *in vivo* It would seem both correct and convenient therefore to apply a single nomenclature to the several phases of this phenomenon, whether seen in the tissues or in isolated blood or bone marrow preparations L E bodies (naked, swollen, amphophilic, leucocyte nuclei) are equivalent to hematoxylin bodies (naked, swollen, amphophilic, mesenchymal cell nuclei), L E cells represent L E bodies ingested by leucocytes or histiocytes

It has been demonstrated that L E bodies are extremely frequent in the tissues of patients with S L E The data of Klemperer et al, suggest that with careful search they may be demonstrated almost invariably (19) These authors found them most frequently in renal glomeruli and in the endocardium, less often in many other sites serous membranes, synovia, lymph nodes, spleen, and the dispersed connective tissue

There are two types of cellular change In the most striking and obvious, naked nuclei are dispersed in large masses and present the alterations ordinarily characterized as pyknosis or karyorrhexis These nuclei are small, dense, deeply basophilic, and appear to break down into small spherules and dust-like debris In the periphery of such foci one may find occasional nuclei having a different appearance—swollen and translucent rather than dense and opaque, amphophilic

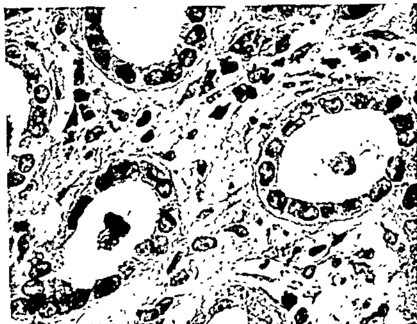


FIG 4 Kidney Tubule at left contains two L E bodies adherent to a desquamated epithelial cell Tubule at right contains an L E cell ×700

rather than basophilic These altered nuclei, violaceous in hematoxylin and eosin preparations, can be equated with the L E bodies of bone-marrow aspirate or blood preparations When phagocytosed by leucocytes in the tissues they are indistinguishable from L E cells The tissue-L E' bodies are most often found as isolated forms in the endocardium, in blood vessels, in the skin, in renal glomeruli (Fig 3), and in serous membranes, unassociated with masses of pycnotic nuclei as described above When L E bodies occur in large, coalescent masses they constitute the hematoxylin bodies of Gross, pictured by him in the endocardium They can occur, however, in other loci—e g in serous membranes (Figs 1 and 2) The older L E bodies lose their Feulgen stainability and gain PAS reactivity (20) It has been suggested by Klemperer that S L E fibrinoid represents aggregated L E bodies depleted of DNA (1) It is also possible, however, that DNA, leaching out of older L E bodies into the surrounding milieu of ground substance adds S L E specificity to locally precipitated fibrinoid It is of interest that L E bodies and L E cells formed in glomerular loops (either from fixed cells or from leucocytes) can be washed into the lower nephron (Fig 4) Presumably they should be found in a concentrated urinary sediment, offering an additional aid to clinical diagnosis

The L E phenomenon—i e, the development of L E bodies, has not been described in any but mesenchymal cells (10) The writer, several times believing he saw the L E transformation in renal tubular epithelial cells, could not ex-

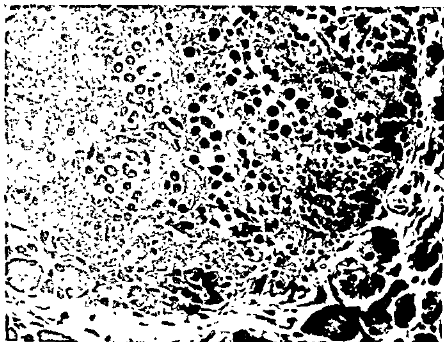


FIG 5 Pancreas, islet of Langerhans L E transformation of nuclei—probably epithelial Capillary dilatation and hemorrhage Fibrinoid masses on right ×350

clude the possibility that these were L E bodies shed from glomerular loops

This led to dilatation, engorge-
farction of whole islets These observations suggest that given a suitable concatenation of cell damage and local hemodynamic disturbance leading to concentration of antinuclear immune bodies (see below), any cell may suffer L E. transformation. It is noted in this connection that complement fixation of specific L E. gamma globulin can be carried out with a range of heterologous and unrelated cells (21).

Until recently it had been urged by Klemperer and his co-workers that the L E. body, whether in tissues or in in vitro blood preparations, was produced by the depolymerization of DNA in the nuclei of mesenchymal cells The studies of Kurnick et al, suggested that the serum of patients with S L E contained a factor which served as the inactivator of intracellular DNAase inhibitor (22) It is interesting that even during the period of preoccupation with the idea of depolymerization of DNA, it was noted that the Feulgen-positive L E bodies also exhibited increased pyroninophilia. This presaged the next steps in our understanding of the L.E phenomenon when vital data was forthcoming from two directions—chemical and immunological.

Godman and his co-workers showed in a series of brilliant, systematic, cyto-

chemical studies of the L.E. phenomenon that depolymerization of DNA is not the basis for the peculiar appearance of altered nuclei in S.L.E. (23-25). They postulated that protein, not normally found in nuclei, enters the latter, displaces histone, and combines with DNA. Reduction in methyl green complexing by DNA in the L.E. body is more apparent than real since stainable anionic sites are either preempted or masked by competing non-nuclear, inflowing protein. Destruction of basic groups in the latter by acetylation frees the dye binding sites and reveals undiminished, fully polymerized DNA.

At the same time, it was suggested by immuno-histochemical techniques that gamma globulin was fixed in phagocytosed L.E. bodies (26). From here it was a short but rational step to the assumption that the "L.E. factor" in abnormal serum is, in fact, an antibody, capable of being specifically complexed to nuclear material. Employing orthodox complement-fixation and absorption methodology Robbins et al., found that when sera from patients with S.L.E. exhibited the L.E. phenomenon they often reacted in vitro with homologous and heterologous nuclei and with various DNAs in accordance with the generally accepted criteria of antigen-antibody reaction (21). Although more proof of this interpretation is required, the evidence is strongly suggestive that the L.E. phenomenon, whether *in vivo* or *in vitro*, indicates "specific" complexing of nuclear material with immune serum protein in the sense of antigen-antibody interaction. The present writer has several times observed a remarkable dissociation between the clinical L.E. test and the post-mortem demonstration of L.E. bodies. In these instances the L.E. test was repeatedly negative when, at the time of death, an extraordinary degree of L.E. body formation was observed in the tissues. This apparent paradox can probably be explained by assuming that massive intravital nuclear fixation of circulating antibody left little or none available for in-vitro demonstration.

It is incumbent on us to reconcile the immunologic explanation of the L.E. phenomenon with the observed anatomical changes. If for the moment, we limit ourselves to a consideration of the cellular alterations only, we find no precedent in general pathology for a phenomenon similar to the L.E. body in form and genesis. It is, indeed, this very uniqueness which stretches credibility. One hopefully searches the considerable literature of transplantation immunity. The rejection of homografts seems fairly well founded in antibody response to antigenic material identified or associated with desoxyribonucleoproteins in the engrafted tissues (27). There has been no description in rejected homografts of any cellular change comparable to the L.E. body. It is of course possible that such alterations have been overlooked.*

THE GRANULOMATOUS MANIFESTATIONS

In 1945 Teilum described two fatal cases of systemic lupus erythematosus in which he found epithelioid cell granulomas and nodular necrosis in serous membranes, lungs, and lymph nodes (28, 29). These changes were very minute,

* How often must we ruefully observe with Goethe, "man sieht nur, was man weiss." Many pairs of eyes had scanned L.E. bodies in tissues many thousands of times without arrest until the discovery of the L.E. phenomenon invited a more searching and imaginative reexamination.

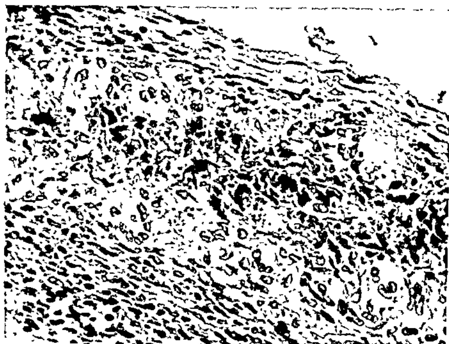


FIG 6 Splenic capsule Epithelioid and giant cell granuloma with central coalescent L E bodies and fibrinoid ×350

though grossly visible, and consisted of foci of "fibrinoid necrosis" surrounded by large, pale, epithelioid cells without caseation, and without eosinophiles He believed these lesions to be not only characteristic but also indicative of the allergic nature of lupus erythematosus He also pointed out that they had not been singled out by previous students of the disease. And for good reason—for this particular tissue expression is most unusual in S L E It may be however, despite its rarity, a significant stigma of hypersensitivity. The writer has observed such lesions in serous membranes and their connective tissue adhesions (Figs. 6, 7), and in the mediastinal and esophageal connective tissues (Figs 8, 9, 10) in S L E They consist of histiocyte-epithelioid cell nodules, with or without giant cells, which may or may not enclose masses of fibrinoid, occasionally compounded with coalescent L E. bodies (Figs 6, 9).

Save for the little understood granuloma of Boeck's sarcoid, tuberculoid lesions generally appear as a local tissue reaction to toxic, or infectious, or foreign material Although tuberculoid lesions of one configuration or another have been noted in hypersensitivity in man (30, 31) and in experimental serum sickness (32, 33), there is no evidence that such lesions are in themselves a primary expression of hypersensitivity Indeed, it is questionable if even the tubercle of tuberculosis is an allergic lesion (34) It appears to the present writer that tuberculoid lesions present themselves in hypersensitivity only when antigen-antibody interaction culminates in precipitation of large, insoluble aggregates which may also include the degraded products of concomitant local tissue destruc-

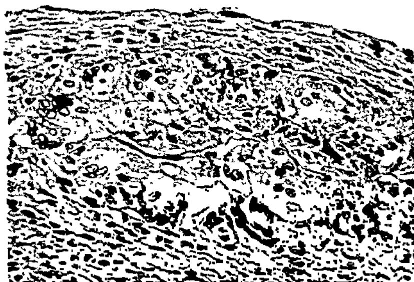


Fig 7
Fibrinoid
Resemblance to foreign body reaction ×[illegible]

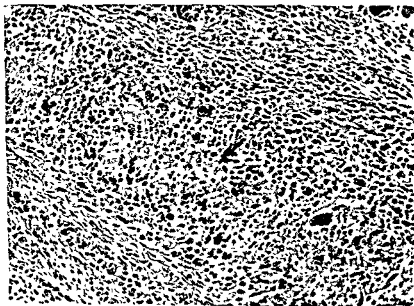


Fig 8 Esophagus Tuberculoid, histiocyte epithelioid cell granuloma in adventitia of esophagus ×165.

FIG 9 Esophagus Histiocyte-epithelioid cell reaction to coalescent L E bodies and fibrinoid ×350

FIG 10 Esophagus, interstitial tissue Tuberculoid, epithelioid-giant cell nodule showing traces of L E substance in center. ×165

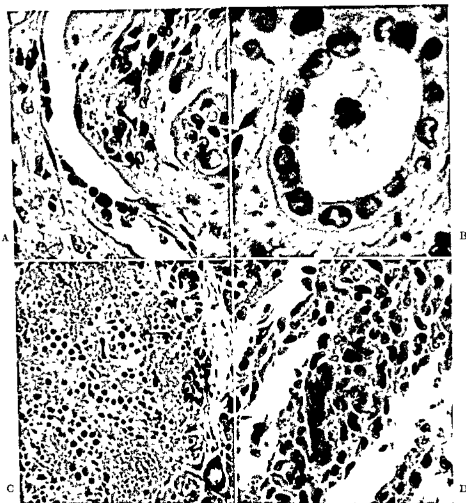


PLATE I

[illegible] ...ented ... Lat ... ...aceous ... ...agocy ... ...in ap- ... ...ation are [illegible] H and E

D Skeletal muscle Intermuscular connective tissue septum shows coalescing, fragmented L E bodies (hematoxylin bodies) with histiocytic and epithelioid cell reaction similar to lesion depicted in FIG 9 H and E

tion. Such conglomerates may thus, because of their unnatural physical or chemical constitution, provoke a foreign body response—i e, a tuberculoid reaction There are some indications that the nature of the local response to antigen-antibody interaction is conditioned by the size and complexity of the precipitated aggregates in passive serum sickness (35) There are other observations which suggest that fixation of complement during certain antigen-antibody interactions results in the activation of ferments from proenzyme complement fractions (36) If such observations can be confirmed and extended, a rational mechanism for the development of such tissue changes as "fibrinoid necrosis" may be elucidated.

CONCLUSION

At the time of the discovery of the L.E phenomenon ten years ago, the constellation of structural changes in S L E had already been fairly well circumscribed and a clinico-anatomical entity well established Despite a mass of accumulated information, no reasonable clue to the pathogenesis of this malady presented itself It was persistently urged in some quarters, however, that S L E was a disease of hypersensitivity This was based particularly on the frequent occurrence of so-called fibrinoid degeneration in the connective tissues, a supposed pathognomonic stigma of allergic inflammation There is not yet any incontrovertible evidence that S L E. is initiated by hypersensitivity There is, however, a rapidly growing body of fact which would seem to indicate that whatever the unknown primary derangement in S L.E, the major, overt, structural manifestations are secondary and based on antigen-antibody interaction

Reference has already been made to the occasional finding of rather massive destruction of cells in many tissues, particularly serous membranes, lymph nodes, and spleen, in which individual nuclei present the conventional aspect of karyorrhexis rather than the L E. alteration The pathogenesis of these changes is not apparent Whatever the cause, be it enzyme or metabolic disturbance, or infection (37) it is not inconceivable that these nuclear changes reflect a pool of unique antigenic material with complex haptenic groups (including DNA and other nuclear substances) available for autosensitization. I would beg forgiveness for interpolating here another speculation. that the patient with S L E has somehow become host to a heterophile system whose antibody has an unfortunate, fortuitous affinity for his own nuclear material.

These lucubrations are consonant with the ideas expressed by Miescher and Vorlaender who consider S L E a disease of unknown cause (38) They do not regard it as an allergic disease proper. Nevertheless, certain manifestations *appear, having the nature of autosensitization, in which antinuclear* immune bodies interact with the nuclei not only of leukocytes but also of other cells, giving rise to the L E bodies in blood and to hematoxylin bodies in tissues As the primary cause of the disease is obscure, so also is the mechanism of sensitization

It is obvious that one of the most immediate tasks in our understanding of

S L E is a search for and characterization of the antigen responsible for the immune phase of this disease

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THE NATURE AND PATHOGENETIC SIGNIFICANCE OF THE L E CELL PHENOMENON OF SYSTEMIC LUPUS ERYTHEMATOSUS

GABRIEL C GODMAN, M D

New York, N Y

INTRODUCTION

Many detailed descriptions of the L E cell and numerous accounts of its diagnostic significance in systemic lupus erythematosus have been published since its discovery by Hargraves et al, (1) It soon became obvious that the hematoxylin stained bodies of the tissues first depicted by Gross (2) and Ginzler and Fox (3) as material of nuclear origin were entirely analogous to the L E bodies found *in vitro* These anatomic observations, which drew attention to a reaction centered in the nucleus, have formed the basis for most of the subsequent research into the pathogenesis of systemic lupus The early characterization by Haserick et al, (4) of a factor in the serum of patients with systemic lupus capable of provoking the L E phenomenon in susceptible cells, and the anatomical and histochemical analyses of the hematoxylin bodies in this disease by Klemperer and his associates (5, 6) gave the prospect of new insight into the nature of this *hitherto obscure disease*

These earlier histochemical analyses of the composition of the lupus body, and therefore hypotheses which depended on them, were based in large part upon histochemical dye-binding methods whose interpretation has since been found more complicated than was assumed in 1950 The L E bodies as well as other tissue lesions in lupus have been re-examined using these and other histochemical techniques, and the process of their formation more closely observed, with consequent revisions of many of our ideas Presently, new insights are being gained in several laboratories from immunological and chemical study of the L E serum factor and its interaction in vitro with various cellular constituents It is therefore timely to review our knowledge concerning the origin, development and composition of the L E body as a key to pathogenesis in systemic lupus erythematosus

MORPHOGENESIS OF THE L E BODY AND L E CELL

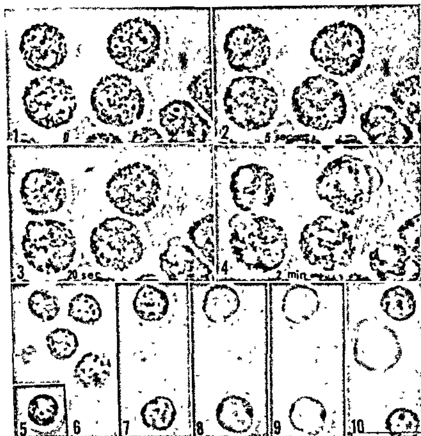
It is now generally held that the nuclei of both mature granulocytes and lymphocytes, normal or leukemic (7–9), as well as the cells of other tissues (10) can undergo the peculiar alteration characteristic of the L E body The cells of other mammalian species are also susceptible to this change (11–13) The appearance of the typical L E cell in conventional preparations, its morphological differentiation from other bodies of somewhat similar form, and the conditions for obtaining these cells for diagnostic use have been documented in an

From the Department of Microbiology, Columbia University, College of Physicians and Surgeons, New York, N Y

ample literature, and are dealt with elsewhere. Of interest in the present context, and ancillary to an understanding of their chemical composition is an accurate account of the morphological changes which formation of the L E cell involves, and the time sequences in which they occur.

In the presence of the L E factor of the serum, nuclei of susceptible cells of isolated nuclei (14) or certain deoxyribonucleoprotein preparations (15) first undergo a peculiar and characteristic alteration, and these are subsequently engulfed by active phagocytes, almost always polymorphonuclear leukocytes, if the latter are present. This two-stage sequence was observed by Rebuck and Berman (16) in a consecutive study of the cells on coverslip windows applied, with L E serum, to the abraded skin of normal human subjects, and has been described in supravital preparations by Rohn and Bond (17–19). These authors, using supravital stains to assist light microscopy, observed that the affected nuclei of mature polymorphonuclear leukocytes first showed swelling and then dissolution of the chromatin pattern, with conversion of the nucleus to an amorphous mass within the original cytoplasmic envelope. They noted that phagocytosis did not occur until this surrounding cytoplasm was at least partially dissolved. In excellent cinematomicrographs recorded through the phase microscope by Robineaux (8, 20, 21), the L.E. phenomenon was studied in greater detail. The nuclear change, which sometimes affected only one lobe, was characterized by loss of the chromatin pattern usually within an intact membrane, this was usually accompanied by isolation of the surrounding cytoplasm. Rifkind and Godman (9) following the sequence of events in the same cells during the L E phenomenon, with particular reference to its primary phase, found that within 5 to 15 seconds of the addition of L E serum to susceptible substrate polymorphonuclear leukocytes, a sudden uniform loss of their chromatin pattern (homogenization) of the nuclei occurred, followed at once by marked swelling and increased density and often at least partial extrusion of the swollen lobes from the cytoplasm (Figs. 1–4). The nuclear membrane remained intact; in the material of these observations the swollen nuclear lobes maintained their identity, each tending to form an L E body (Fig. 4), although it has been noted by Robineaux, that fusion of the altered nuclear substance into a large amorphous mass sometimes took place in his specimens. Lymphocyte nuclei underwent similar changes following exposure to L E serum (Figs. 5–10), although more slowly. The surrounding cytoplasm in all cases was passively displaced by the altered expanding nucleus or L E body, and took no visible part in and made no contribution to the formation of the L.E. body; the phenomenon appeared to concern only the nucleus.

Phagocytosis of the L E body can occur only after some of the altered nuclear material is presented to the active phagocytic cell at least partly free from its surroundin[illegible] of lobes [illegible] The ma- [illegible] r leukocytes. The photographs of Robineaux et al, (8) show clearly that the phagocyte ingests the altered nuclear material alone, and not the residual cytoplasm. It



Figs 1 to 10 represent phases of the L E phenomenon made with the technique of Davis and Eisenstein (26) All are phase contrast photographs made at a magnification of X1500
Fig 1 Polymorphonuclear leukocytes at the instant of addition of L E serum showing

are in the field

has been commented upon (4, 6) that the L E. transformation in vitro may take place within some minutes, indeed the very great rapidity with which the nuclear changes can occur under the influence of the L.E factor is noteworthy: once initiated, the whole transformation of the polymorphic nucleus to the completed L E. body may require no longer than 30 to 60 seconds (9).

It has usually been considered necessary to injure or alter in some way cells intended as substrate for the action of L E factor in order to produce good yields of L.E cells Most of the different procedures devised for improved clinical diagnostic tests have had as their basis various methods of effecting such injury, e g., clotting (22, 23), rotating with glass beads (24), drying (25, 26). Robineaux et al, (8, 21) however, have reported the successful use of living leukocytes washed with a physiological saline solution as substrate cells for the L E transformation. While the mere withdrawal of blood into glass vessels or the anoxia prevailing in coverslip chambers, might in itself be thought to effect a minimal injury to some leukocytes, the reported L E. transformation of the nuclei of presumably viable cells is of considerable interest, both in its implications for the *in vivo* formation of such bodies in lupus, and in posing the problem of how the active gamma globulin factor might gain access to the living nucleus.

In permitting detailed visualization of the entire sequence of the L E. phenomenon, the stages of which could be compared with the appearance of stained preparations, phase microscopy has provided valuable information. However, it remains useful chiefly as a modality for investigating the cellular phenomena themselves and offers no apparent advantage over conventional L E. preparations for more routine diagnostic purposes Phase microscopy alone has been applied by some (21, 27) where the more easily observed stained preparations would have afforded more readily interpretable information.

COMPOSITION OF L E AND HEMATOXYLIN BODIES

Some observers of the L.E phenomenon have referred to the nuclear changes as a "lysis" (16–18, 8, 20), a visual impression which was consonant with our previously held conception of the chemical nature of the L E. bodies. The hematoxylin bodies were known to have originated from cell nuclei soon after their discovery (1, 2) and the finding that they, and L E bodies, contained deoxyribonucleic acid (DNA) was confirmed by ultraviolet absorption and the Feulgen reaction in the histochemical analyses reported in 1950 by Klemperer and coworkers (5, 6) These investigations depended on measurement of the manner in which the DNA of the hematoxylin bodies bound the basic dye methyl green, which, under certain conditions can bind selectively and stoichiometrically to DNA (28–38)

In the experiments of Kurnick (30) and Kurnick and Mirsky (31) on DNA samples *in vitro* it was shown that depolymerization of the DNA reduced its affinity for methyl green. On this basis, because of the reduced stainability of the hematoxylin bodies in the tissues with methyl green as compared with normal nuclei, their DNA was regarded as having undergone a change in the nature of depolymerization This interpretation of the significance of methyl green uptake

has since been modified the binding of this dye by nucleic acid in tissue specimens is now known to be influenced principally by such factors as fixation (34–36), the presence of cations (30, 31, 35, 37), pH (37), and most important, it is impaired by competitive interference of protein associated with DNA (34, 38, 39). Control of some of these variables permits us to make use of quantitative measurement of methyl green binding to gain information on the amount of DNA and its relationship to protein (39).

In more recent microspectrophotometric measurements (40–42), it was confirmed that methyl green staining of L.E. bodies and hematoxylin bodies was uniformly depressed as compared with control nuclei. To assess the effect of protein on methyl green binding by DNA in hematoxylin and L.E. bodies, methyl green uptake in the same bodies was measured before and after destruction by acetylation of the basic groups of protein which compete with basic dye for the phosphoryl groups of DNA. In contrast to the small increase in methyl green stainability effected by acetylation of protein basic groups in normal control nuclei, this procedure resulted in almost a 100 per cent increase of the apparent amount of methyl green which the DNA of L.E. bodies was capable of binding (Table I). It would thus appear that about half of the stainable sites of DNA in lupus bodies were masked by protein. The Feulgen reaction for the deoxypentose moiety of DNA, which is relatively insensitive to those changes in degree of polymerization of DNA or to its relation to proteins which affect methyl green staining, is therefore useful as a reference against which to compare such staining properties of DNA as its methyl green uptake. In most normal nuclei, such as those from which L.E. bodies originate, the ratio of the amounts of methyl green to Feulgen revealed DNA is about 1.0. The amount of methyl-green-stained DNA

TABLE I

Mean amount of methyl green and Feulgen dye bound in L.E. bodies derived from lymphocytes

Measurements of free (non phagocytosed) L.E. bodies in L.E. preparations made with lymphocytes from a patient with chronic lymphatic leukemia. The data illustrate the effect of competing protein groups, which are destroyed by acetylation, upon the binding of methyl green by DNA in lymphocytes and L.E. bodies respectively. Acetylation results in similar Feulgen : post acetylated methyl green ratios for both, indicating that DNA is not depolymerized in L.E. bodies.

	Lymphocytes	L.E. Bodies
(No. measured)	(20)	(20)
Methyl green	16.7 ± 0.5	11.9 ± 0.3
Me Gr after acet	17.8 ± 0.8	23.1 ± 0.6
Feulgen	19.9 ± 0.4	21.3 ± 0.5
Post acet Me Gr / Me Gr	1.06	1.94
Feulgen / Me Gr	1.19	1.79
Feulgen / Post acet Me Gr	1.12	0.92

TABLE II

Mean amounts of DNA and protein in L E bodies derived from lymphocytes

Measurements of free (non-phagocytosed) L E bodies in L E. preparations derived from lymphocytes The Feulgen data show that DNA is not lost in the course of the L E transformation The marked increase of naphthol yellow S binding and Millon staining indicate the marked increase in total protein content in the formation of L E bodies The decline and disappearance of alkaline fast green and in Sakaguchi staining in L E bodies suggests a loss of histone

	A *Lymphocytes*	B *Early L E Bodies*	C *L E Bodies*	Ratios	
				B/A	C/A
Feulgen	15 4 ± 0 4	18 0 ± 0 5	17 7 ± 0 4	1.17	1 15
Naphthol yellow S	14 5 ± 0 6	23 8 ± 1 1	36 5 ± 1 1	1 64	2 54
Alk fast green	19 0 ± 0 4	5 5 ± 0 6	*	0 29	—
Sakaguchi	3 1 ± 0 2	1 5 ± 0 1	*	0 48	—
Millon	2 2 ± 0 2	—	5 7 ± 0 4	—	2 75

* Indicates below measurable limits

after acetylation of competing protein groups, compared with the amount of DNA measured in the same bodies by means of the Feulgen reaction (i e, the Feulgen:postacetylated methyl green ratio) would indicate whether there is any residual decrease in methyl green uptake by DNA, i e, which cannot be accounted for by the presence of competing protein If there were, this ratio would be reduced in comparison to control nuclei Measurements showed that the Feulgen:postacetylated methyl green ratios of both L.E bodies and control nuclei tended to approach 1 0 (Table I) Thus, the decreased methyl green stainability of L E bodies could be satisfactorily accounted for by the effects of protein interference resulting from an association of a protein with the DNA of L E bodies not manifest in normal nuclei The data gave no evidence of an altered state of the DNA itself, such as depolymerization Entirely analogous results were obtained with hematoxylin bodies, the tissue counterparts of L E bodies (42) Moreover, comparison of the total relative amounts of Feulgen-revealed DNA in L E bodies with those of normal nuclei of the type from which they were derived (lymphocytes) showed that there was no significant loss of DNA in the process of the L E transformation (Table II)

It was thus evident from these data that in the nuclear alteration of lupus, the protein component of the affected nuclei rather than the DNA itself was changed in kind and/or amount The "total amount" of protein present in objects such as L E bodies and nuclei can be estimated by [illegible] metric measurement of the colored comple[illegible] binding and from the Millon reaction [illegible] (dipo-tassium flavianate) has been shown by [illegible] to combine stoichiometrically with the available ε-amino groups of lysine, the guanidyl groups of arginine, and the imidazole group of histidine residues in fixed protein, thus affording a valuable measure of the number of protein basic groups free to accept the dye in

any site Application of this procedure made it evident that the number of such groups was more than doubled in the L E body as compared with the lymphocyte nucleus from which it originates Quantitation of the product of the cytochemical Millon reaction (for histone plus nonhistone proteins (44)) gives a relative measure of the tyrosine residues of protein Since this reaction reveals another grouping, and is independent of some of the ionic and electrostatic interferences attendant upon acid and basic dye binding, it is a valuable complement to other cytochemical estimates of the amount of protein present With this procedure a more than two-and-one-half fold average increase in protein tyrosine residues was measured in the formation of an L E body from a nucleus These data, which show increases in reactive groups, suggest an augmentation of the total amount of protein in such transformed nuclei That this is indeed the case has been demonstrated by Rifkind and Godman (9) by means of interferometric microscopy in which it was determined that L E bodies had an average anhydrous mass (52 8 $\times$ 10^{-12} gm) two-and-one-half times greater than that of control lymphocyte nuclei (21 7 $\times$ 10^{-12} gm)

These determinations established that a marked augmentation in total amount of protein occurs in the L E transformation of nuclei Further differences in protein composition between nuclei and the L E bodies were disclosed by the cytochemical test for histone proteins (41) These basic proteins are normally closely linked to DNA in all intact cells, where, owing to their high isoelectric points, they can be selectively demonstrated and quantitated (after removal of nucleic acid) by staining with the anionic dye fast green FCF, at high pH The phagocytosed bodies of the L.E cells and of hematoxylin bodies were almost always devoid of stainable histone, while the free L E bodies varied from diminished stainability to complete absence of coloration Microphotometric estimations of total histone in nuclei in the course of the L E change showed this diminution to occur very early These results were interpreted to indicate that the L E change entails either a loss of histones or else a masking of their available basic groups by some substance not normally present in nuclei Arginine residues as determined by the Sakaguchi reaction (which is not subject to the same ionic electrostatic or steric factors affecting acid or basic dye-binding), are reduced nearly in half in the earliest L E bodies, and much further in the mature L E bodies This fact would tend to favor the hypothesis that histones are displaced from their link with DNA by a protein normally foreign to the nucleus, and thence more easily lost However, there is said to be no apparent increase in arginine in supernatant L E serum over substrate leukocytes (47), and since some histone stainability may sometimes be detected in L E bodies, the hypothesis must also be entertained that the histone remains, but that its combining groups are preempted or shielded and so prevented from accepting the dye, a condition analogous to that of the DNA Hematoxylin bodies of the tissues invariably contained no basic protein of the histone type as detected by these methods (42). From these results it was concluded that:

1 The DNA of the L E body is not detectibly depolymerized or significantly reduced in amount in the formation of the L E body from the leukocyte nucleus

2 There is a more than twofold increase in total measurable protein and hence anhydrous mass in the formation of the L E. body due to influx from without (i e , L E. serum) of a protein normally foreign to the nucleus.

3 Consequent on the entry of this protein, histones are possibly displaced from their normal combination with DNA, and subsequently either lost or masked by protein, and the DNA becomes associated (combined) with the new protein

4 The nucleoprotein masses (L E bodies) formed in this way in systemic lupus are deposited in the tissues as the so-called hematoxylin bodies.

Insight into the nature of the incurrent protein reacting with cell nuclei was afforded by studies in at least two laboratories of the L E. cells and free bodies by means of the immunohistochemical techniques of Coons and his collaborators (48) In these investigations fluorochrome-labelled antisera to normal human gamma globulin were allowed to react with L E. cells, the sites of brilliant fluorescence then representing the localization of gamma globulin in the cells In such preparations nuclei undergoing the L E change (free L.E bodies), and the L.E. cell inclusions (phagocytosed bodies) fluoresced brilliantly, while normal nuclei, nuclei incubated with control (nonlupus) sera, or those stained with heterologous nonhuman antigamma globulins or in which the antigen (globulin) had been blocked failed to fluoresce, thereby indicating the presence of gamma globulin in the nuclei which have undergone the L.E transformation (49, 50).

That the L E serum factor has an affinity for nuclear nucleoprotein is further suggested by the immunohistochemical technique, which showed the nuclear localization of fluorescent anti-human gamma globulin in the nuclei of normal autologous, homologous and heterologous tissues which had been exposed to L E serum (51–53) The nonspecificity of the substrate nuclear material is in accord with the same nonspecificity of substrate cells in eliciting the L E. cell phenomenon It has been further shown by Friou (54) that the fluorescent L.E. globulin from all cases of lupus erythematosus, irrespective of its L E cell forming capacity, is bound to either extracted or artificial nucleohistone preparations The demonstration of gamma globulin in L E bodies strongly suggests that this protein, putatively that measured by Godman and Deitch (41), which enters the nucleus from L E serum to bring about the L E change, might be antibody But it does not by itself constitute final proof that the gamma globulin in this site is indeed immunologically reactive

NATURE OF THE INTERACTION OF L E FACTOR AND NUCLEAR CONSTITUENTS: THE SEROLOGY OF SYSTEMIC LUPUS

At first, following the previously held concept that the L.E and hematoxylin bodies contained partially depolymerized DNA, it was hypothesized that in systemic lupus the supposed depolymerization of DNA was effected by an intracellular deoxyribonuclease (since serum DNase could not be implicated) released from an intracellular inhibitor (55) by the entry of a serum protease, whose penetration into the cells was presumably facilitated by the postulated action of the L E. factor on the cell surface (56–58) The bases of this group of hypotheses

which may be referred to as the "enzyme theory" are not tenable because more recent evidence has corrected the earlier idea and has shown that the DNA of L E. bodies is not detectibly depolymerized (40–42), but also because it is now well established that the L E factor (not itself a depolymerase) reacts directly with the nuclear constituents

Miescher and Fauconnet (59) first showed that the L E cell-forming factor of L E serum and globulin was absorbed by isolated homologous and heterologous nuclei, and that nuclei charged with this factor could be identified in the antiglobulin consumption test and by phagocytosis (14) The absorbed L E factor could be at least partially eluted from nuclei and not unexpectedly was found to be a gamma globulin with L E. activity (14, 15, 59) The nucleoprotein (nucleohistone) extractible from nuclei by 1 M NaCl also reacted with the L E. serum factor, but neither nuclei nor nucleoprotein could do so if their DNA had been removed by deoxyribonuclease (DNase) treatment (15) These evidences that a factor in L E gamma globulin which is absorbed by nuclei reacts with DNA were further reinforced by the finding of definite precipitin and complement fixation reactions obtained with lupus sera (but not others) and "purified" DNA (60–64) These precipitation reactions, which were obtained equally with DNA of human, animal and bacterial origin, could be demonstrated by Seligmann (64) with very dilute solutions by the Ouchterlony gel-diffusion method, the ring test, the method of passive hemagglutination, and in immunoelectrophoresis. Between 3 and 15 gamma of DNA per ml L E serum was necessary to exhaust the precipitin The precipitation reaction was specific for preparations of DNA and did not react with RNA, in L E sera giving this reaction complement fixation could almost invariably be found (61, 64) L E sera are also apparently capable of inhibiting bacterial transforming principle (i e , DNA) from acting (66) The DNA precipitating and complement fixing "antibody" of L E serum has been characterized by both Seligmann (64) and Deicher, Holman, et al , (63b, 65) as capable of giving a precipitin-curve with a prozone, equivalence zone, and zone of antigen excess, it appears to move as a fast (gamma 1) globulin (66) and to come down with the 7S fraction in the ultracentrifuge

From the nature of these reactions it seemed reasonable to assume that one was dealing with an antibody directed against DNA (61, 64, 65) The serum factor giving precipitation and complement fixation tests with DNA was a gamma globulin It did not resemble a histone (64), and precipitation with DNA was conducted at a high pH in which nonspecific electrostatic or saltlike combination could be minimized (65) The objection that the serum factor might be reacting with protein impurities which accompany most ordinary preparations of DNA [illegible]

quantities of DNA (64) However suggestive the evidence in favor of the antibody hypothesis, final proof of the immunological nature of these reactions should include faithful reproduction of similar phenomena in animals Animals immunized with leukocytic components (67–70), nuclei (68, 69, 71, 72) and nucleo-

protein, (65, 72) have not developed serological patterns quite characteristic of lupus or antibodies reacting with *DNA alone*, nor have the sera of rabbits immunized with leukocytes given rise to appearances generally acceptable as typical L E cells, although interesting ("pseudo L E." (73)) phagocytic phenomena have been observed However Miescher (71, 72) has claimed production of nuclear changes closely resembling the L E. alteration with immune sera against nuclei or nucleoproteins Moreover, although it has been reported that DNA may act as an antigen (74, 75) these results have not been satisfactorily reproduced by other investigators (64, 76) and it remains doubtful that DNA *per se* can act as an antigen, or that experimental immunization with nucleoprotein produces antibodies to DNA

More extensive experience with the complement fixing reactions of L E serum and nuclear components indicated that the L E cell forming factor appeared to be different from that responsible for DNA fixation (63), subsequent research chiefly in Kunkel's laboratory by Holman, Deicher and Robbins (65) has shown that whole groups of complement fixing serum factors, reacting with different nuclear constituents may appear in systemic lupus, and that these groups may have different patterns in different patients These factors may be variously directed against whole isolated nuclei, nucleohistone, DNA preparations, histone, and/or saline non-nucleoprotein extracts of nuclear material. different patients with systemic lupus possessed differing capabilities of reacting with these various constituents The sera of some patients, capable of forming L.E cells, could reportedly react with nuclei, nucleoprotein and histone, but not with DNA, while sera of other patients could fix complement with nucleoprotein and DNA, but not with histone (65)

Some information about the relationship of some of these antinuclear serum factors has been afforded by absorption and elution experiments The relationship of the complement fixing factor reacting with DNA to the L.E cell forming factor is of particular interest The available evidence has indicated that these are not identical After exhaustion of the precipitins of L E. sera by addition of DNA it still remains possible to elicit the L E phenomena (27, 56, 63–65, 77) As noted, the sera of certain patients giving the L E. cell phenomenon contained no demonstrable precipitin (64), or complement fixing factor (65) for DNA

Eluates obtained by treatment of the L E. serum-DNA precipitates with 2 M NaCl or with deoxyribonuclease were alleged by Seligmann and Robineaux (27) to contain the anti-DNA precipitin and also to be capable of inducing the L E phenomenon, but only when mixed with normal serum. Holman, Deicher, et al, (65) have been unable to duplicate these results and are unable to verify that the L E cell forming factor is one which can combine with *DNA alone*. They note, as do Hymans and Schuit (77), that nucleoprotein, but not DNA alone, was capable of completely absorbing the L E. cell forming factor from L E sera in a reaction which did not necessarily fix complement: both the DNA and histone were found necessary for this reaction, nor was histone released by the new combination The discrepancy might be explained by the possibility that Seligmann's DNA preparations contained small quantities of protein The

end point of Seligmann and Robineaux (27, 64), in which the L E change is routinely detected in fresh cells with the phase microscope, should also be checked with histochemical methods to verify the nature of the changes, and to permit comparison The L E serum-nucleohistone precipitate yielded complement fixing gamma globulin factors, but little L E cell forming factor after DNase digestion The L E cell forming globulin could be released from the remaining residue or from L E serum absorbed on nuclei by heating it to 56°C (65) These properties would seen to differentiate the L E cell factor from the other antinuclear factors of lupus, especially in its dependence upon the DNA-protein link for reaction, since it apparently does not react with DNA alone.

The L E cell factor of the serum, correctly identified by Haserick et al., (78) as a gamma globulin, was supposed by them to be "immunologically distinct" from other gamma globulins Seligmann and Hanau (79) and Hijman and Schuit (77) have taken exception to this interpretation Indeed, present evidence would agree that the L E cell factor is itself antigenically like other normal antibody gamma globulins It is said to reside in the Cohn II fraction of plasma (80) Larson (47), using the separation methods made possible by the cellulose cationic exchange column has isolated a gamma globulin which apparently is immunologically (as judged by gel-diffusion band) and electrophoretically homogeneous, moves as a 7S fraction in the ultracentrifuge, and which is capable of giving the L E cell phenomenon and a positive latex test (agglutination with nucleoprotein coated latex) This globulin is said to be chemically differentiable from other gamma globulin by its markedly low N/P ratio (47)

The possibility that the reactions described are combinations with an unusual globulin, but lacking immunological specificity, although remote, has yet to be completely excluded With these objections in view, the hypothesis of the occurrence in systemic lupus erythematosus of a group of serum antibodies capable of reacting with the constituents of cell nuclei would nevertheless appear at present to be the most reasonable, factually consistent and heuristic conception

PATHOGENIC SIGNIFICANCE OF THE SEROLOGICAL ALTERATIONS IN LUPUS AND OF THE L E BODY

While the idea of a disordered immune state as a mechanism in the pathogenesis of systemic lupus had previously suggested itself, interest in this possibility was renewed by recognition of the frequent occurrence of biological false positive serological tests for syphilis (13), and especially by attention to certain hematological manifestations which are seen in some cases of lupus In particular, the occurrence of hemolytic anemia, with red blood corpuscle autoagglutinins and positive Coombs test (13, 81–83), thrombocytopenia and purpura (13, 83–88) and leukopenia (13) have been recorded, and the remarkable readiness with which some patients with S L E develop antibodies against blood corpuscle antigens, and the frequency of transfusion reactions in them have been the subject of comment (13, 89, 90)

consumption) tests (14, 94, 95), leukoprecipitins (64, 94, 96), and antileukocyte complement-fixing factors (94, 97) against leukocyte cytoplasmic antigen in lupus patients who had not been transfused have been documented in detail. These manifestations, which are invoked to explain the hematological signs of the disease, have been taken, together with the L.E. phenomenon, as evidence for the autoantibody or autoimmune theory of lupus (81, 64, 98–102). It is most often postulated that in some manner the patient's own cell constituents become antigenic and gain access to the antibody-forming cells, with the production of a variety of circulating antibodies directed against constituents of the patient's cells. A number of "antibodies" to nuclear nucleoprotein and protein are apparently formed among which the L.E. cell factor, albeit the most constant, is one.

While iso- and autoantibodies to cells, particularly hematic elements, are known to occur in several conditions, it was thought that the antinuclear factor was specific to systemic lupus erythematosus. Many of the reports which have appeared describing L.E. cells in other diseases (101, 103–105) have been doubted especially with regard to the validity of the diagnosis of the L.E. cell. This issue cannot be discussed in detail here, but it should be remarked that confusion might be avoided if these cells were examined not only in conventional preparations, but also with some histochemical methods, such as methyl green affinity and alkaline fast green staining. The occurrence of the L.E. cell phenomena in certain cases after administration of hydralazine (106–108) and in rheumatoid arthritis (109–113) remain problems, in certain cases of chronic hepatitis (lupoid hepatitis) with characteristically elevated globulins, it seems to have been more convincing (114–117) [but see (118)].

This finding is of nosological interest in the light of the recent report by Gajdusek (119) of complement fixing reactions between normal tissue antigens or "reagins" and gamma globulin of some patients with systemic lupus erythematosus (in 9 of 11 cases), lupoid hepatitis (in 3 of 4 cases), macroglobulinaemia, (in 2 of 5 cases), and chronic hepatitis (in 11 of 25 cases). Besides the fixation of complement, the participation of gamma globulin, the stability of the reaction at 56°C., and the occurrence of apparent prozones in antigen titrations were adduced as evidence for the immunologic nature of these reactions (119). It is, however, necessary to bring even more rigorous proof in order to exclude the occurrence of some nonimmunologic reactivity. These reactions could not be elicited against autologous antigens prepared with the patient's own tissues removed at biopsy (120), a fact which has been interpreted by Mackay, Larkin and Burnet to signify that the part of the antibody population of these patients having 'specificity' (highest affinity) for the autologous antigen have been absorbed out of the circulation, and that somehow a spectrum of homologous reactivity persists in the serum. However, it also seems possible that autologous tissue antigens failed to react *in vitro* because they had already been saturated with antibody *in vivo*.

From these varied data there emerges the tentative concept of a category of disease, of which lupus would be one, characterized by the presence of a spectrum of globulins having many characteristics of immune bodies, which have

autologous and heterologous affinity for various tissue constituents the sources and natures of which may differ in individual cases Whether or not such a category of disease will prove to have reality, and whatever the relationship of systemic lupus to the other disorders named in this connection, it remains clear that in systemic lupus serum globulin is formed having a range of reactivities with tissue components most constant and characteristic of which, so far revealed, are the constituents of the nucleus Both the origins and reason for this disorder, and its pathogenetic consequences remain obscure We do not know precisely what relation all the manifestations of disease, clinical, serological and anatomical bear to one another In considering the serological changes, the L E cell phenomenon which depends upon it, and some resulting tissue changes, we are dealing with but two links in a probably long chain of events, the other parts of which remain to be discovered

To explain the occurrence of globulins, presumptively antibodies, which react ✓with nuclear and/or other cellular constituents, it has been conjectured that

1 autologous tissue components may become antigenic through some modification (somatic mutation of a mesenchymal cell (120)) involving loss of "recognition units" (100, 119), alteration by combination with foreign substances (? haptens) has also been postulated,

2 these antigenic materials gain access to antibody producing sites,

3 antibody populations or gamma globulins of varied nature, not conforming to standard pattern, are released which could combine with other autologous, homologous or heterologous tissue constituents (120)

Other theories involve immunization by foreign nucleoprotein and formation of cross-reaction antibodies (53)

Concerning these speculations there is little exact knowledge, we do not know why patients with lupus respond to antigenic stimuli so readily, what qualitative differences there are in their antibodies or why females are so much more apt to develop this disease than males (Dameshek believes that sensitization occurs during menstruation (102)) The mere presence of the L E cell factor per se *in the circulation, and in all probability also the precipitating and complement-*fixing factors already referred to, is seemingly not pathogenic, at least for a limited time Its transplacental passage and its appearance in the blood of the infant for periods up to seven weeks, with well-marked capacity for L E cell formation in the infant's blood, resulted in no apparent disease (121–123)

The relationship of the serologic alterations and of the L E cell phenomenon to some of the lesions in the tissues of patients with systemic lupus erythematosus *as classically described by Gross (1) and especially* Klemperer, Pollack, and Baehr (124) while still unclear, have been somewhat more enlightened by recent studies The nuclear alteration of the L E change is regarded by most clinical observers not only as specific, but also as demonstrable at some time in almost every case of systemic lupus (101) That the L E phenomenon takes place in vivo is suggested by the finding of L E cells in freshly drawn untreated blood of patients (125, 126), in the tissues at autopsy in one case (127), and in the observations of its occurrence in viable cells (8, 21) *Hematoxylin bodies*, which are discrete or conglomerate deposits of the altered nuclear material, have been shown experi-

mentally by German (128) to be capable of deriving from embolization of swollen leukocytes which have undergone the L E transformation It is also very likely that some are formed in situ from fixed tissue cells It is obvious from a comparison of the chemical characteristics of the fresh L.E body and of the hematoxyphil masses that the latter have undergone considerable change during their sojourn in the tissues. For example, fresh L E. bodies stain metachromatically and fail to react with the PAS procedure (40, 42), while hematoxylin bodies are not metachromatic (42), may show diminished Feulgen stainability and are strongly stained in the PAS reaction (42, 129–131), changes which point to the probable addition of protein and of a PAS-demonstrable carbohydrate, and to subsequent loss of nucleic acid from the original nucleoprotein material.

Klemperer (127), and Gueft and Laufer (129) have postulated that with the degradation of these bodies and further loss of DNA from them, the protein residues remain as masses indistinguishable from the fibrinoid or hyaline deposits. From these authors' evidences, this interpretation of the origin of the fibrinoid would appear to be rather more applicable to the thrombotic intravascular masses especially in the glomerular loops than to the material in other loci designated "fibrinoid" In systemic lupus, such eosinophilic materials of arterioles

terials called fibrinoid in lupus have an identical origin. Immunohistochemical (see 132), histochemical (133, 134) and pathological (135) studies of lesions associated with fibrinoid change in various diseases indicate that they are not chemically identical in all cases Plasma proteins, in lupus, gamma globulin, evidently take part in the formation of fibrinoid substances. Of their possible reactivity with extracellular components of the connective tissues, where these masses are often found, nothing is specifically known, but the possibility that a transudation of some protein from the blood and its reaction with materials of the ground substance accounts for fibrinoid alteration of the connective tissue has been put forward (135, 136) It is not improbable that among the various tissue-reactive components in lupus serum, some will be found which combine with some of the still incompletely defined protein and polysaccharide materials constituting the connective tissue ground substances.

The significance of these serological and histological changes for the understanding of the whole morbid process in lupus remains to be elucidated (137), but it is already clear that disclosures made in pursuit of an understanding of the L.E phenomenon and the tissue lesions of systemic lupus erythematosus have assumed a more general importance in pathology, and promise to have ever-widening implications in lupus and in other related systemic diseases

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THE BLOOD IN SYSTEMIC LUPUS ERYTHEMATOSUS*

STANLEY L LEE, M D

AND

BARUCH J DAVIS, M D †

New York, N Y

Alterations of cellular constituents of the blood during the course of systemic lupus erythematosus have been recognized since the earliest descriptions of the disease Changes in the plasma proteins were not recognized until much more recent times, and it is only since the description of the L E cell phenomenon that the possible pathogenetic importance of the plasma protein abnormalities has been emphasized

Several excellent recent reviews have discussed the blood changes in S L E Complete compilations of the world literature may be found in several recent monographs (1–5) No effort to duplicate these contributions will be made here Rather, the present communication will limit itself, on the basis of the pertinent literature, and personal experience, to discussion of those changes in the blood proteins and formed elements which have particular clinical or pathogenetic importance

RED CELLS

Historically, anemia was the first hematic manifestation of S L E to be recognized, it is mentioned in the earliest clinical descriptions of the disease by Kaposi (6). Most patients with S L E are more or less anemic when first examined Anemias associated with S L E can be broken down pathogenetically into three types, in a given patient at a given time, one, two, or all three mechanisms may be at work The first type, which is almost universally operative, is normochromic or slightly hypochromic, mild or moderately severe with normal or diminished reticulocytes and an apparently active bone marrow Although no physiologic studies of this anemia have been published, there seems no reason to believe that it differs in any respect from the anemia associated with other systemic diseases (arthritis, cirrhosis, tuberculosis, neoplastic disease) (7) Bone marrow depression, due in large part to a disturbed protein metabolism and diminished hemoglobin synthesis associated with constitutional illness, is the major cause of this anemia There is also a hemolytic component, red cell life span averages ½ to ⅔ of normal

A second cause for anemia in S L E is the more specific bone marrow depression associated with azotemia This is ordinarily a feature of late stages of the

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† Aided by a Stipend of the Altrua League, Inc , Brooklyn, N Y

From the Department of Medicine, Division of Hematology, The Mount Sinai Hospital, New York, N Y

disease, when advanced renal disease has become prominent. Recent studies suggest that the bone marrow hypoplasia of azotemia may be due to lack of production of the specific erythropoietic stimulating factor ("erythropoietin"); here too, there is a hemolytic component to the anemia (8).

Finally, the full-blown picture of acquired hemolytic anemia may occur. This is usually an early manifestation of the disease, and is in fact, the presenting manifestation in about five per cent of cases. It does not differ clinically or in pathologic physiology from other acquired hemolytic anemias, with jaundice, splenomegaly and severe anemia as outstanding features. In almost all cases it is possible to demonstrate globulin "coating" of the patient's red cells by means of the direct anti-globulin technique, "autoantibodies", usually of the "warm" type, may be demonstrable in the serum. These patients, despite extremely active hemolysis, do not have hemoglobinuria. Very rarely another type of hemolysis occurs in which no serologic mechanism can be demonstrated, and in which hemoglobinuria is prominent.

Treatment of anemia in a patient with S.L.E. is only important when the anemia is the major manifestation of the disease; this in fact only occurs either in the chronically anemic patient or in one with a severe hemolytic process.

In the case of the anemia of azotemia, no treatment other than blood transfusion is apt to be effective at the present time. Erythropoietin is not available in a form suitable for administration to humans, if and when such a preparation becomes available, it may be of great value in this situation.

Blood transfusion in any patient with S.L.E. should only be resorted to only under the most pressing indications. A tendency to form antibodies to blood group substances which are not usually strongly antigenic (i.e., factors like those in the Kidd and Duffy systems and the minor Rh types) is characteristic of this disease (9–10). The number of stimuli by these substances should therefore be kept at a minimum for each patient.

In the patient with hemolytic anemia, treatment with ACTH or corticosteroids is usually very effective, with rapid decrease in the rate of hemolysis and improvement of hemoglobin level. Blood transfusion here must be restricted to the patient whose hemoglobin is dangerously low. In addition to the considerations discussed in the preceding paragraph, the rate of hemolysis in the actively hemolyzing patient is directly related to the concentration of red blood cells, so that transfusion often defeats its own purpose.

WHITE CELLS

Persistent leukopenia is mentioned prominently in most discussions of hematic changes in S.L.E. Reduction in the number of white cells is, however, rarely of high degree. Neutropenia is uncommon, most of the reduction being effected by a marked lymphopenia. Leukocytosis occurs in response to infections, pregnancy and other unknown stimuli. Before the advent of the L.E. cell phenomenon the leukopenia of S.L.E. was of diagnostic importance, nowadays a low white blood count would be, at best, a lead pointing toward S.L.E.

Reliable information as to the mechanism of the white cell depression of S.L.E. is lacking. Several investigators have found evidence, by one or another

immunologic technique, of "antileukocytic antibodies" in the sera of patients with S L E (11, 12) Lapin, using an extremely meticulous technique, finds a very high incidence of an unidentified substance which is capable of immobilizing and killing white cells (13, 14) One difficulty in correlating the studies of these workers with the clinical facts is that all of them have used polymorphonuclear leukocytes as substrate cells, while the striking cytopenia of S L E involves the lymphocytes

In summary, leukopenia (lymphopenia) is very common in S L E, but is of little physiologic importance, of limited diagnostic value and of unknown origin

PLATELETS

Slight to moderate thrombocytopenia is common in S L E Fifty per cent or more of patients show some degree of platelet depression at some time during their course Severe thrombocytopenic purpura is not common, the incidence in The Mount Sinai Hospital series is only 5 per cent It may, however, be the presenting manifestation of the disease, such was the case in one of our patients

The mechanism of thrombocytopenia in S L E is not clear Bone marrow examination invariably demonstrates increased numbers of megakaryocytes showing poor platelet formation, exactly as in idiopathic thrombocytopenic purpura (ITP) Since several studies have put the humoral theory of ITP on a firm footing, attempts have been made to demonstrate anti-platelet "antibodies" in S L E as well (15, 16) Agglutination and anti globulin techniques, although successful in the hands of some workers, have been difficult to apply and have given equivocal results The more recent use of anti-globulin consumption tests, and precipitin and complement fixation techniques has given convincing demonstrations of the presence, in S L E serum, of substances capable of reacting specifically with human platelets (11) Clarification of the possible role of such substances in causing thrombocytopenia in living patients has yet to be made

Severe thrombocytopenic purpura, although not common, may occur at any time during the course of the disease and may, on occasion, be the dominant clinical manifestation The management of thrombocytopenic purpura secondary to S L E is essentially the same as the management of idiopathic thrombocytopenic purpura A good response to adrenocorticomimetic hormones may be anticipated For the occasional patient with severe purpura with few other manifestations of S L E it is worth noting that splenectomy is usually an effective therapy A recent report suggests that splenectomy may accelerate the course of S L E but such has not been the general experience (17, 18) At The Mount Sinai Hospital in the past ten years, there have been three splenectomies for thrombocytopenic purpura secondary to S L E In all three cases, permanent remission of thrombocytopenia occurred One patient died four years after splenectomy, the other two are under treatment for S L E four and eight years respectively after operation

PLASMA PROTEINS

It has become increasingly apparent in recent years that alterations of the plasma proteins are of great significance in S L E These alterations involve,

in ascending order of probable importance, fibrinogen, albumin, alpha globulins and gamma globulins

Fibrinogen

Increased circulatory concentration of this protein occurs in most inflammatory conditions. S L E. appears to be no exception Hyperfibrinogenemia is probably the major contributing cause of the rapid erythrocyte sedimentation characteristic of the disease, other clinical or pathogenetic significance is doubtful.

Albumin

In the later stages of S.L E., and especially in the presence of significant renal involvement, a reduction of the plasma albumin is noted. This is frequently severe enough to be associated with edema, the nephrotic syndrome in the course of S L E is discussed elsewhere in this series of papers (19).

Hypoalbuminemia in S L E probably represents a combination of two lesions: failure of synthesis associated with the ravages of a chronic disease, and loss into the urine.

Alpha globulins

It is possible with present day techniques, to distinguish thirteen individual alpha globulin fractions in human serum, but the significance of pathologic variations among these is unknown (20) Many of these alpha globulin components contain high percentages of carbohydrate and hence belong to the group of "glycoproteins" or "mucoproteins."

There is little question that there are profound disturbances among this group of proteins in S L E Reiner was among the first to notice elevation of the alpha-2 globulins (21) This finding has subsequently been confirmed by others; alpha-1 globulin increase has also been prominent. Greenspan has found a high level of "mucoprotein" in patients with S L.E ; Boas & Soffer found high serum hexosamine levels (22, 23) Both of these latter findings probably involve substances in the alpha-globulin group.

The single most important quantitative component of this group is the serum haptoglobin- a protein (or, more probably, series of proteins) whose variations in disease have been studied by Jayle and by Allison and Blumberg (24, 25). This is a glycoprotein which has the ability to bind hemoglobin; it has been found by these writers to be elevated in a variety of pathologic states The serum haptoglobin has been found to be elevated in twelve out of fourteen cases of S.L E. (26)

It is possible that these alpha-globulin deviations in S L E may prove to be of great significance, at present it can only be noted that they exist.

Gamma globulins

Profound changes in the plasma gamma globulins occur during the course of S.L E These changes are quantitative and qualitative. There is usually, at the time of diagnosis, a definite elevation of the gamma globulin level; as the disease progresses, there is a tendency for further rise (3, 27). Evidence is accumulating

that these gamma globulins are composed of numerous varieties of proteins resembling antibodies but having unusual and abnormal specificities

Disturbances of the gamma globulins in S L E have both practical and theoretic importance, and so deserve consideration at length here

Quantitative Changes

Characteristically, the gamma globulin level is high (27) This may be detected clinically by electrophoresis or by Kunkel's zinc sulfate turbidity (28) The finding is almost universal and so of some diagnostic importance Occasionally, however, normal or low gamma globulin is found This usually, if not always, is associated with considerable renal involvement It is possible that hypogammaglobulinemia in S L E with nephropathy is due entirely to urinary loss of gamma globulin, however, observations on one patient lead us to believe that this simple explanation is inadequate

Elevation of gamma globulin, as well as hypoalbuminemia and hyperfibrinogenemia, contributes to the rapid rate of erythrocyte sedimentation which is usually found in this disease This constellation of plasma protein changes is probably also responsible for the abnormal "liver function tests" (cephalin-cholesterol flocculation and thymol turbidity) which are characteristically found (29) The p-toluene sulfonic acid test recently described by Jones & Thompson is another flocculation reaction which probably has the same degree of specificity (30, 31).

Qualitative Changes

When tested by ordinary physico-chemical methods, the plasma gamma globulins of S L E do not behave abnormally Electrophoretically and chromatographically, they are normally heterogeneous (32) in contrast with the homogeneous paraproteins of myeloma or Waldenstrom's syndrome. In the ultracentrifuge, the vast preponderance sediments with a Svedberg number of 7 and usually only a normally small proportion has a sedimentation constant of 19 (33) Despite an early report suggesting that S L E gamma globulins have specific antigenicity subsequent efforts by several groups to demonstrate this have failed (33–35) It now seems most likely that S L E gamma globulin cannot be distinguished from other human gamma globulin by its antigenicity for other animals

With regard to their antibody content, however, S L E gamma globulins exhibit the most striking, unusual and abnormal behavior Chief among the antibody (or antibody-like) activities which have been studied is, of course, the L E cell factor In addition, patients with S L E exhibit several other gamma globulins which act like abnormal auto-antibodies Finally, there is suggestive evidence of a distortion of antibody response to antigens of external origin

These qualitative abnormalities of the gamma globulins in S L E will be discussed in some detail, since they have considerable interest both for the clinician and for the investigator

L E CELL PHENOMENON

In 1948 Hargraves and his associates reported the presence of an abnormal leucocyte in the bone marrow aspirate from patients with S L E (36) The cell

was a phagocyte containing a homogeneous inclusion body which stained reddish blue with azure-eosin. Because of its unique appearance, the frequency with which it was found in S.L.E., and its apparent specificity, the cell and its inclusion body was named the "L.E. cell."

The L.E. cell phenomenon, more than any other clinical or laboratory characteristic of the disease commands the attention of physicians and research workers for three reasons. First, because it is of great diagnostic value. Second, it is a phenomenon reproducible in vitro and thus easily amenable to laboratory analysis. Finally, the factor responsible for L.E. cell formation may play a role in the clinical course of the disease.

Description of the L.E. Cell

The morphologic and tinctorial criteria are as follows: The presence of one or more inclusions in a phagocyte, usually a neutrophilic leucocyte. The inclusion body is round or oval, completely homogeneous and compresses or displaces the phagocyte nucleus to the periphery. When stained with azure-eosin the inclusion body is a pale blue with a more or less pink component. It must be distinguished from nucleophagocytosis in which the inclusion may be an intact nucleus or an entire cell, and in which the nuclear inclusion takes a deep blue stain with identifiable chromatin structure. It must be distinguished from erythrophagocytosis in which the inclusion body has no blue color (the use of dark blue filters can make this distinction difficult).

Associated constantly with L.E. cells in positive preparations are two other phenomena, "rosettes" and "free L.E. bodies." Rosettes are aggregates of leucocytes which surround a degenerating cell or a portion of nuclear material. "Free L.E. bodies," or "globs," are extracellular fragments varying in diameter from about three microns up to ten to fifteen microns and having the appearance and staining characteristics identical with those of the inclusion body of the L.E. cell. In deciding whether or not a given L.E. cell preparation is positive, although "rosettes" and "globs" are suggestive, they are not sufficient by themselves since a variety of non-specific artefacts can produce them.

Incidence of Positive L.E. Cell Preparation in S.L.E.

The L.E. cell phenomenon has been demonstrated in from forty to one hundred per cent of patients with S.L.E. (37). The more recent series, however, list figures well over ninety per cent. The higher percentages are in part the result of technical factors: improved methods and more tests per patient. They may also, in some instances, reflect the clinician's increasing dependence upon the test as a criterion for the diagnosis. Thus any assessment of the frequency of the L.E. cell phenomenon in S.L.E. is limited by the fact that there is no other absolute criterion by which a diagnosis of S.L.E. can be made.

Clinical remissions, whether spontaneous or induced by steroid therapy, are generally, but not always associated with a reduction in the degree of positivity of the L.E. cell phenomenon. However, the positivity or negativity of the preparation is a poor index of the clinical status of the patient and is of unreliable prognostic value.

L.E Cell Specificity

The early literature on the L E cell mentions many different diseases associated with positive L E cell preparations As experience with the test increased, the number and variety of false positive tests diminished, and one must assume that the early instances of nonspecificity were probably the result of inadequate experience with the test or, more rarely, the coincidence of another disease and unrecognized S L E

At the present time the problem of "false" positivity is restricted to a few diseases and the observations are made and reiterated by experienced physicians Positive L E cell preparations have been reported in liver disease, chronic hydralazine toxicity and rheumatoid arthritis

Liver Disease

A search of the available literature reveals less than fifteen cases of positive L E cell preparation in patients with chronic liver disease proved by biopsy (Laennec's cirrhosis, postnecrotic cirrhosis and active chronic hepatitis (37–42) Four of the reported cases presented clinical or postmortem evidence of S L E Another three cases failed to disclose evidence of S L E on postmortem examination Of these, however, one was found to have diffuse myelomatosis, no histo-chemical studies were performed to determine if the L E cell inclusions were nucleoprotein or amyloid In another case the photograph of the L E cells was not convincing

Until further follow-up reports are available and histochemical and serologic studies are performed, the occurrence of the L E cell phenomenon as a manifestation of liver disease must be viewed with skepticism

Hydralazine

On occasion, the syndrome of chronic hydralazine toxicity is indistinguishable from S L E (43) In all cases reported cessation of drug therapy was followed by remission of the syndrome No spontaneous exacerbations are reported, no postmortem examinations are reported In some, but not all of the cases there was a history prior to drug therapy suggestive of S L E

The L E cell phenomenon in these cases of hydralazine toxicity is indistinguishable by conventional methods and also by serological and histochemical techniques, from the L E cell phenomenon in S L E

In an attempt to reproduce the syndrome in laboratory animals, Comens administered the drug to seven dogs (44) Six of the animals are reported to have developed positive L E cell preparations and on postmortem examination glomerular lesions were found Examination of the photographs does not allow the unequivocal conclusion that the cells are L E cells It would be of great interest to repeat the experiment in order to study the sera and tissues of these dogs by the latest histochemical and serologic methods

Rheumatoid Arthritis

The L E cell phenomenon is positive in from zero to twenty-seven per cent, of patients with rheumatoid arthritis (37, 45–47) Analyses of reported series shows that those series with a high percentage of positive tests contain more cases which clinically show evidence of systemic disease suggestive of S L E Those with a lower percentage contain more cases of rheumatoid arthritis with

few or no signs of extra-articular disease It appears that between the extremes of mild rheumatoid arthritis and acute fatal S L E there exists a spectrum of cases which display, to variable degrees, the characteristics of both diseases

In rheumatoid arthritis, absolute diagnostic criteria are lacking Typical rheumatoid arthritis may occur as a manifestation of S.L E ; and, conversely, cardiac, renal, and serous membrane lesions have been described in rheumatoid arthritis

There is a converse to the existence of "false positive" L.E cell tests in rheumatoid arthritis Blood from patients with S L E. sometimes shows the presence of the "rheumatoid factor " The "rheumatoid factor," widely held to be specific for rheumatoid arthritis, has been shown by Franklin and associates to be a gamma-one macroglobulin (22 Svedberg units) (48). The same or similar protein has been shown to occur in sarcoidosis, kala-azar and liver disease (49). It thus differs from the abnormal gamma globulins of S.L.E. under discussion and belongs to a different class of proteins. Its biological significance is obscure Present methods for its identification vary widely in different laboratories. Whether positive tests for rheumatoid arthritis in cases of S.L E are due to the same "rheumatoid factor" as found in cases of rheumatoid arthritis is not clear.

Thus, interrelationships between S L E. and rheumatoid arthritis exist on several planes their significance cannot yet be evaluated

L E Cell Techniques

Many methods for demonstrating L E. cells have been published Each technique has its proponents who believe it more sensitive and reliable Comparisons of techniques have yielded conflicting results and there is no unequivocal evidence that one is better than another. Improperly employed, all methods will fail Without begging the issue, it must be concluded that experience and facility in performing the test and discrimination in reading the test slide are more important at present in determining reliability and sensitivity than is the particular technique employed

Certain essentials must be met by any method. Deliberate traumatization of the substrate cells, either chemical or physical, increases the number of L E cells If L E plasma is employed minimal amounts of heparin should be added since excessive concentrations of heparin depress or prevent the formation of L E cells

Mechanism of the L E. Cell Phenomenon

Within a short period of time after the original observation of the L E. cell phenomenon (36), it became apparent that the phenomenon could be demonstrated by simple *in vitro* techniques and that the essential factor contributed by the patient with S L E was a blood gamma globulin substance (50, 51). It is now known that the L E. cell phenomenon depends upon three components. Blood serum or plasma of a patient with S L E. containing a specific gamma globulin fraction, the *L E. cell factor*, when incubated with *substrate leucocytes*, converts the nuclei into swollen amorphous masses that are then engulfed by *viable phagocytes* to produce L.E cells

By systematically altering the components participating in the reaction, it was possible to define the necessary conditions for the formation of the L E cells.

L E. Cell Factor

The L E cell factor is a gamma globulin On starch block electrophoresis the factor migrates with the faster fraction of the gamma globulin On ultra-centrifugation the factor sediments with the bulk of the normally occurring gamma globulin (7 S), (33) Chemical separation of the factor from serum is achieved by employing the routine methods for gamma globulin precipitation, however, unless the method is a "mild" one the separation is attended by loss of activity The factor is heat labile, heating serum at 56°C for one hour destroys all activity. The factor is stable indefinitely once frozen but activity is quickly lost on repeated freezing and thawing of L E serum

Substrate Leucocyte

Human white cells and dog bone marrow cells are used most frequently although cells from a number of species are sensitive to the factor Hematoxylin body formation, which is the analogue in tissues of the L E cell phenomenon, has been observed in postmortem material to involve all types of cells of mesenchymal origin (52) Epithelial cell nuclei, both normal and neoplastic, have been shown to be susceptible to the L E cell factor (53, 54)

Evidence strongly supports the hypothesis that an intact viable leucocyte is resistant to the factor since chemical or physical trauma deliberately inflicted increases the rapidity of L E cell formation, the number of L E cells per total leukocyte population and the sensitivity of the test Types of trauma include freezing and thawing, mechanical crushing and sieving of a blood clot, mechanical disruption by glass beads, air drying on a microscope slide and chemical trauma with quinacrine (54–60) In those techniques in which there is no deliberate trauma, the long incubation period probably accounts for cell alteration because of an unfavorable metabolic milieu

Phagocytes

Substrate cells once acted upon by the factor are engulfed by viable phagocytes Nothing is known as to the nature of the stimulus for phagocytosis except that it resides in the substrate-serum factor complex Washed free of the L E serum the substrate cells will still undergo phagocytosis when placed in contact with suitable phagocytes

Biochemical Basis of the L E Cell Phenomenon

The L E cell phenomenon demonstrates the existence of an abnormal gamma globulin which is able to produce morphologic changes in leucocytes The nature of these changes and the mechanism by which they are produced have been the subject of extensive investigation These investigations have been conducted in two fields histochemical and serologic

The histochemical studies are extensively reviewed in another paper in this series, they will only be summarized very briefly here

In their first report on the L E cell, Hargraves and his associates stated that the inclusion body was Feulgen positive and hence contained desoxyribose nucleic acid (DNA) (36) Later studies of the tissue hematoxylin bodies by

Klemperer and his associates and of the L.E. cell inclusion by Lee, Michael and Vural were interpreted as showing that the DNA of these bodies was partially depolymerized (51, 61). Gueft and Laufer then found that the protein content of the L.E. bodies was different from that of normal nuclei (62). The histochemical studies have now culminated in the work of Godman and Deitch (63, 64). They have shown that leucocyte nuclei contain increased amounts of protein following incubation with L.E. cell serum; that there is no histochemical evidence of depolymerization of DNA, and finally that as incubation of S.L.E. serum with nuclei proceeds nuclear histone seems to disappear.

The earliest serologic studies after the demonstration of the L.E. cell factor by Haserick and Bortz proceeded from the *supposed* histochemical evidence of DNA depolymerization (50). These studies which dealt with possible relationships between L.E. cell factor and depolymerizing enzymes (DNA-ase) are now only of historical interest (65, 66).

The modern era in the serologic investigation of the L.E. cell phenomenon was ushered in by the studies of Miescher and Fauconnet (67). By incubating S.L.E. serum with large quantities of leucocyte nuclei prior to performing the L.E. cell test, they were able to inactivate the serum. They further demonstrated that during incubation with nuclei detectable amounts of gamma globulin were lost from the serum. These findings directed Miescher to apply to this system the "antiglobulin consumption" test (68). With this technique, material eluted from nuclei previously incubated with serum containing the L.E. cell factor was shown to contain gamma globulin. Thus the gamma globulin lost from the serum was demonstrated to have been bound to the nuclei.

Holman and Kunkel showed that the material bound to the nuclei incubated in S.L.E. serum was itself capable of inducing the L.E. cell phenomenon after elution from the nuclei (33). They further found that the reaction between S.L.E. gamma globulin and nucleoprotein fixed complement.

Seligmann employing the Ouchterlony agar diffusion technique, observed precipitin lines when S.L.E. serum diffused into purified DNA from nucleoprotein (69).

Thus it became increasingly evident that the application of immunologic methods provided a fresh and fruitful approach to the analysis of the gamma globulin dysproteinemia of S.L.E.

Subsequent studies, employing serologic and precipitin techniques demonstrated that S.L.E. gamma globulin may contain several components characterized by their affinity for different substrates (11, 35, 70–74). One component is readily absorbed to nuclei and nucleoprotein; one to DNA, and a third to histone. The affinity for nuclei, nucleoprotein and DNA is not restricted to leucocyte substance but can be demonstrated with nuclei from a number of organs as well as from different species. The components are not all constantly present in every S.L.E. serum but vary from patient to patient.

The L.E. cell factor is associated with the gamma globulin component which is strongly adsorbed to nuclei and nucleoprotein. It is possible that the L.E. cell factor is not a single physically and chemically homogeneous protein but

rather a group of proteins that have a strong affinity for nuclear material. Whether it can be bound by native DNA in the absence of the protein moiety remains to be tested. Strong evidence argues against the possibility that desoxyribonuclease participates in the reactions.

OTHER ABNORMAL ANTI-BODY-LIKE GLOBULINS

False Positive Serologic Tests for Syphilis (S T S)

Until the recent development of serologic reactions using Treponema pallidum as the antigen, the serologic diagnosis of syphilis was based on the reaction of serum with an antigen derived from beef heart. The common occurrence of false positive reactions to this latter antigen in sera from patients with S L E was first recognized by Coburn and Moore in 1943 (75). They demonstrated by electrophoretic separation that the factor in S L E blood was predominately in the gamma fraction with only a small component migrating with the beta globulin fraction. A further distinction was noted when upon heating to 56°C the luetic antibody decreased in potency, while the factor in S L E blood gained in potency. The clinical application of the Treponema Pallidum Immobilization test (T P I) now provides a simple and certain means to verify this difference.

The reported incidence of false positive S T S in S L E is variable, depending in part how vigorously the search is pursued. When batteries of tests are performed and the T P I test employed to exclude syphilis, the incidence ranges between twenty and thirty per cent.

In the latest available long term follow-up of individuals who have the false reactor substance, there were reported 148 cases followed from one to twenty years (76). Ten per cent of the number developed S L E, seven per cent developed rheumatoid arthritis, and forty-five per cent had evidence of S L E or a "collagen vascular disease". Stress is laid upon the observation that an individual may develop a false positive S T S years before there is clinical or laboratory evidence of S L E.

Circulating Anticoagulant

Many reports have noted the appearance of a bleeding disorder in S L E distinct from thrombocytopenia. In all the reported cases this has been due to the presence of a substance in the affected plasma which inhibits the second stage of blood coagulation, namely the conversion of prothrombin to thrombin by thromboplastin (77–81). The abnormality appears to reside in the gamma globulin. Whether it combines with thromboplastin or prothrombin to accomplish its end is not clear (78, 79). Possibly anticoagulants in different patients have somewhat different specificities. In any case, this material appears to be another of the abnormal antibody-like substances which characterizes S L E.

The circulating anticoagulant of S L E occurs most frequently in minimal sub-clinical concentration. In The Mount Sinai Hospital series, over twenty per cent of patients tested showed some abnormality. In only one case however, could clinical bleeding be ascribed definitely to its presence. An anticoagulant

of this specific type is, however, of diagnostic importance, since it has very rarely been reported in other conditions

Anti-RBC, WBC and Platelet Substances

These have been discussed in the section on hemocytologic changes. They occur with great frequency in S L E , but so far have not been differentiated from similar activities occurring in other diseases.

DISCUSSION

The manifestations of S L E. in the blood are thus seen to be manifold and profound All cellular components and most of the protein fractions are sometimes or always involved Which, if any of these disturbances are of fundamental importance?

The cytologic disturbances can be dismissed in this regard, since they are always symptomatic Hyperfibrinogenemia and hypoalbuminemia likewise can be ascribed to known or suspected mechanisms and hence placed in their roles as secondary phenomena. Alterations of the alpha globulins may be of very great importance pathogenetically, but what we know of them so far indicates that in S L E they follow a pattern similar to that seen in some other chronic diseases. lymphomas, tuberculosis, rheumatoid arthritis.

Gamma globulin abnormalities characteristic of S L E are, however, unique, it is possible to establish the diagnosis from a sample of blood entirely on the basis of its content of specific abnormal "auto-antibodies". So far, the list of anti-substances includes proteins active against DNA, DNA-histone, histone, cell nuclei, leukocytes, platelets, red blood cells, thromboplastin, and beef heart antigen This profusion of antibody-like activities directed against "antigens" which, for the most part, are normal body constituents, gives rise to speculation in two distinct directions

First, the clearly demonstrable *in vivo* effects of the "auto-antibodies" so far described are very few and relatively unimportant. Such relationships as the anti-RBC factor in hemolytic anemia, anti-platelet factor in thrombocytopenia and anti-coagulant in hemorrhagic disorders are fairly clear but of peripheral interest The L E cell factor (or factors) has not been shown to have any physiologic effects *in vivo* Nevertheless, the existence of this multitude of anti-substances leads one to suspect that many other analogous proteins may exist A circulating substance active specifically against glomerular basement membrane might, if it could be demonstrated, provide a partial explanation of the nephropathy of S L E Similarly, an antisynovial membrane, or anti-hyaluronic acid might define the arthropathy of this disease Attempts to demonstrate these or other activities which might have important pathogenetic effects should clarify the question of whether the "auto-antibody" theory of S.L.E. has any validity

The second line of speculation concerns more fundamental matters. If one accepts, for the moment, that "auto-antibodies" are the immediate causes of the manifestations of S L E (a statement clearly not proved on the basis of present

knowledge alone) the real problem in S L E concerns the production of "auto-antibodies" It has been suggested that repeated stimulation by bacterial infection may eventually give rise to a spectrum of anti-bacterial antibodies among which may be an anti-bacterial-DNA, and that with further stimulation the anti-bacterial-DNA develops broader specificity so that eventually an anti-any-DNA is produced (11) Broadening of antibody specificity with hyperimmunization is something which has been demonstrated in animals An alternative hypothesis would invoke a metabolic defect of the antibody-forming tissues which results in subtle distortions of antibody response A streptococcal antigen might, because of faulty ribose nucleic acid synthesis in the host, invoke an antibody not against the streptococcus itself, but against something quite different—thromboplastin, for instance

A number of hypotheses intermediate between these extremes might easily be tailored to fit the pitifully few facts available The design of experiments which might help to define the problem more clearly is difficult, since so little is known of mechanisms of normal antibody synthesis One problem which demands investigation, however, concerns the response of S L E patients to selected heterologous antigens

In conclusion, numerous studies over the past eight years have demonstrated that in S L E a large variety of antibody-like substances occur which have individual specificities against many different normal body constituents That these antibody-like proteins are the direct cause of the important clinical and anatomical manifestations of the disease is an attractive hypothesis for which proof is so far lacking Finally, should overwhelming evidence for this hypothesis be forthcoming, the fundamental problem in S L E will be the discovery of the reason for abnormal antibody production

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THE CLINICAL FEATURES OF SYSTEMIC LUPUS ERYTHEMATOSUS

SAUL JARCHO, M D
New York, N Y

INTRODUCTION

This essay is devoted to the clinical depiction of systemic lupus erythematosus (S L E) Discussion concerning the pathology, the hematic disturbances and the treatment will be presented by other contributors in the present symposium

Systemic lupus erythematosus is a serious constitutional disorder which in fullest efflorescence usually affects the skin, mucosae, serous membranes, small blood vessels, endocardium, connective tissue, kidneys, brain and blood. Untreated cases ordinarily are fatal, a few go into spontaneous remission

The cause of S L E is unknown During the twelve and a half decades which have elapsed since the earliest descriptions, the disease passed from the realm of dermatology to the more comprehensive realm of internal medicine and morbid anatomy At present, the most promising studies are those of cytopathologists and cytochemists (1), who seem likely to reveal either the basic cause or some of the fundamental mechanisms Discovery of the cause will inevitably make possible a more exact delimitation of the disease than can be given today and will authoritatively resolve the question of the relation between S L E. and discoid lupus as well as the relation between S L.E. and other diseases in which connective tissue is systematically affected.

DISCOID LUPUS

Inasmuch as there are competent observers who maintain that S L E is in some way akin to discoid lupus, the latter condition will be described here, although it is properly outside the scope of the present discussion

Chronic discoid lupus erythematosus is a disease which appears in the form of one or more mildly indurated scaly reddish plaques Often these clear in the center but extend at the margins. The central cleared area tends to become atrophic and to show telangiectasia. When the silvery scale is lifted it typically brings with it adherent keratotic plugs. Obstruction of hair follicles and sweat ducts is highly characteristic The lesions show marked chronicity but may heal and leave a pigmented residue The commonest site of occurrence is the face, especially the cheeks, but also the nose, ears, and lower lip Lesions may occur symmetrically on the cheeks and may extend over the bridge of the nose, producing a conformation like the shape of a butterfly. The term vespertilio is often used in European descriptions and provides a welcome alternative designation for those who are becoming tired of the conventional lepidoptera The scalp is commonly affected, alopecia being a frequent consequence. The lesions of chronic discoid lupus may spread over the chest, back and extremities, producing the so-called chronic disseminated lupus erythematosus. This is less common

than the circumscribed variety The lesions retain the traits of the chronic discoid form.

Dermatologists also recognize special types of lupus known as lupus erythematosus profundus and tumidus These have been attributed to localization of the infiltrate in the deeper and intermediate layers of the skin respectively (2)

Constitutional symptoms are rare in chronic discoid lupus In chronic disseminate lupus symptoms are mild and consist mainly of arthralgia and lassitude. Since chronic discoid and chronic disseminated lupus tend to be ignored by internists and research workers, little fundamental information is available as to whatever physiological and biochemical disturbances may accompany these diseases Montgomery has made the important observation that in one third of a series of thirty cases of acute disseminate lupus erythematosus the disease started as the chronic discoid type (3) Lejhanec and Lejhanec reported a case of what was probably discoid lupus which underwent acute exacerbation (4) Autopsy disclosed lesions similar to those often encountered in S L E, viz, pneumonitis, fibrinous pleuritis, and verrucous endocarditis In some cases of discoid lupus Rein and Kostant found hyperglobulinemia and biologic false positive reactions for syphilis, these facts lend additional support to the belief that discoid lupus may be related to S L E (5)

SYSTEMIC LUPUS ERYTHEMATOSUS

Incidence

S L E most often occurs in young women but it has been found also in children and middle-aged persons, and it may occur in males It has been observed repeatedly in Negroes of either sex (6)

There is a marked tendency for the disease to appear or to recrudesce after the patient has been exposed to sunlight Hence acute cases tend to be relatively common in spring and summer Exacerbation may also occur after exposure to artificial ultra-violet rays Focal infection has been incriminated but not convicted Allergic persons show no special predisposition to S L E Haserick has reported a few examples of familial occurrence (7-9)

The Quarterly Cumulative Index Medicus lists reports of the disease from almost every country which contributes to the medical literature, but no recent worldwide analysis of geographical distribution is known to the present author It would seem, for reasons already given, that such analysis should emphasize the parameters of solar radiation, cutaneous pigmentation, and perhaps altitude Study of a generous sample of case reports from foreign countries reveals no regional peculiarities in the clinical picture

Twenty years ago systemic lupus erythematosus was regarded as a rarity and cases almost always found their way to staff meetings and clinico-pathological conferences During the last two decades, and especially during the last five years, the disease has been recognized with greater accuracy and ease than ever before Diagnosed cases may now be found in the medical service of any large general hospital in the United States

At any time, months or years after its debut, discoid lupus may flare into

acute S L E (10, 11) This fact fortifies the opinion that the two diseases are related At present it is not known whether *all* cases of discoid lupus are susceptible to acute exacerbation. Indeed, the transformation is uncommon Actinic radiation, chrysotherapy and surgical operations are usually incriminated as precipitating causes of the abrupt changes (12)

Clinical Features

Since S.L E is a systemic affliction in which lesions may occur in many different organs and organ systems, individual cases show great diversity in onset and evolution. Often the presenting symptoms are malaise, lassitude, low fever, and chilliness or true chills The case thus may be classified among fevers of unknown origin Another common mode of onset consists of fever and arthralgia, or of fever, arthralgia and pleurisy. In other cases the initial symptoms may assume the guise of nephritis or thrombopenic purpura or hemolytic anemia or even idiopathic epilepsy. Skin lesions may make their appearance at any point in the course or may be absent during the entire illness. Fever is rarely absent in the untreated case and is a rough index to the acuteness and severity of the morbid process

A few persons have been found who appeared to be in good health but who had a positive Wassermann or Meinecke test without history or physical signs of syphilis and with negative response to the treponema immobilization test It has been shown that some of these persons later developed the clinical signs of S L.E (13).

Although the fully developed case of S L E , like the early case, may show a predominance of symptoms and signs referable to one organ system, involvement of several systems is almost invariable in late stages. The unfortunate victim usually has high fever, pleurisy or pericarditis, pneumonitis, widespread cutaneous eruptions, mucosal ulceration, anemia, and azotemia. To this complex agony a bacterial complication such as sepsis or bacterial endocarditis may be superadded not long before the end.

In the pre-steroid era there were a few patients in whom the decline of the fever and the fading of the eruption heralded a remission which might last for many years Such remissions can occur repeatedly in a single patient It was usually thought that a person who had acute S.L.E. was unlikely to live more than eighteen months, whereas subacute cases might be protracted to about three years Both estimates were defeated by occasional favorable cases At the present time it is believed that steroids will force acute symptoms into clinical quiescence but there is no unanimity as to whether these drugs prolong life It is my impression that they do. An especially interesting study of the prognosis of S L.E will be found in the paper of Merrell and Shulman (14)

Skin and Mucosae

The cutaneous lesions of S L.E. are extremely varied; this fact contributes alike to the interest of the problem and to the perplexity of the physician The most typical lesion is an elevated, sharply marginated erythematous area situated on the malar eminences and the bridge of the nose. Confluence of

these areas produces the familiar butterfly or bat contour. In acute cases the erythematous areas often lack sharp delimitation, especially at onset. Erythematous lesions frequently appear on the forehead, ears, eyelids, chin, and the so-called flush area of the neck and manubrial region The redness tends to stop at the frontal hair-line and at the orbital margins. The arms, forearms, trunk, palms, and soles may be affected The erythema often presents a distinct violaceous or lilac hue, especially on the face The appearance may be that of persistent intense redness, hence the terms *erysipelas perstans faciei* and *erythema perstans faciei*, used by the great dermatologists of the past The skin of the fingertips and that around the nailbeds tends to swell and turn red or purple Deep tender macules may appear on the palmar surfaces of the terminal phalanges and elevated red patches are formed on the dorsa of the fingers The erythematous involvement of the fingers is usually greatest at the distal end

Petechiae or even large hemorrhages may be found, especially on the extremities Occasionally vesicular or bullous lesions complicate the scene It is not rare for the eruption to have the characteristics of urticaria or erythema multiforme (15) *Tumulty has reported cases of S L E in which* typical erythema nodosum was present and several which resembled scleroderma (16) Variety is characteristic of any group of cases and of many individual cases. Instances have been reported in which the skin presented nodular lesions like papulonecrotic tuberculids (17, 18) The scalp may be affected in S L E, but this is rare (19).

The skin lesions itch in a minority of cases Scaling occurs but is neither frequent nor prominent.

Subsidence of the eruption is apt to leave a brownish stain, especially on the face. Atrophy and telangiectasia occur, but are less common and less severe in S L E. *than in discoid lupus*

It is important to recognize that involvement of the skin provides no index to the intensity of the visceral disease The skin may be clear even in cases which end fatally (20).

In cases of moderate or great severity the mucous membranes are usually affected Most often the changes take the form of shallow ulcers on the palate, fauces, pharynx, or, much less often, the tongue; erythema, hemorrhage and telangiectasia may be present at the same time The ulceration may be complicated by moniliasis The lips tend to become swollen, sore and crusted Epistaxis is not unusual The ulcers greatly augment the suffering and also impede the administration of food and fluids Ulceration of the genitalia occurs and is often overlooked

In a small number of cases one or more indolent lesions of discoid lupus, of the type described in a previous paragraph, may be present for years before the constitutional symptoms of S L E make their debut In such cases the discoid lesions tend to become bright red and engorged when the acute stage supervenes.

Joints

Most lupus patients have arthralgia at one time or another. Pain in the joints is often the first symptom and may appear years before any other com-

plaint, it is apt to be accompanied by mild stiffness, especially of the fingers and knees Pain is common during the onset of acute and subacute stages of the disease Frequently the joints ache without tenderness even when the disease appears to be in remission. In the severe cases redness and synovial effusions develop, hence the erroneous diagnosis of acute rheumatic fever may be offered Periarthritis, tenosynovitis, and myositis are common.

Harvey, et al , have noted that even the temporo-mandibular joint may be involved (21) This detail should be of special interest to old clinicians who regard temporo-mandibular arthritis as evidence of Neisserian infection.

The appearance of the joints presents no special traits by which the diagnosis of S L E can be made The synovial fluid may yield a positive L.E. test. Suppuration and ankylosis are not part of the clinical picture.

In a few who suffer from S.L E. the joints acquire the appearance typical of rheumatoid arthritis. In such cases it may be impossible to decide whether the patient has one disease or two.

Serous Membranes

Lesions of the major serous membranes are conspicuous in the morbid anatomy of the S L E and are an important determinant of the clinical picture. Acute fibrinous pleuritis with pain and dyspnoea occurs in a large proportion of the severe cases Effusion is common Pericarditis, somewhat less frequent than pleuritis, may produce small or large effusions, which are sometimes loculated Both pleural and pericardial fluid may yield a positive L E test (22)

The abdominal serous membranes are not exempt from the disease To this fact is ascribed the ill-defined abdominal pain which so often occurs In some cases the morbid process manifests itself as perisplenitis or perihepatitis, characterized by pain and tenderness in the upper abdominal quadrants. Acute surgical disease of the abdominal viscera may be simulated.

Lymph Nodes, Spleen, Blood

General adenopathy is frequently but not invariably present. The nodes usually are not tender, matter, or indurated. The adenopathy may occur with or without mild degrees of splenomegaly When these signs are accompanied by hemorrhagic phenomena the false diagnosis of primary blood dyscrasia may be hard to resist.

As previously stated, some persons whose troubles start with thrombopenic purpura later develop characteristic manifestations of S L.E. In such cases splenectomy may be of temporary benefit but is certainly not curative. Thrombotic thrombopenic purpura has been suspected of being a congener of S L E (23, 24)

Leukopenia, definite but not extreme, is typical of S L E The differential white count may be normal or may be shifted to the left Haserick observed that in the severe untreated case of S L.E eosinophiles are few or absent in the peripheral blood and that these cells appear after treatment with steroids is begun (7) Leukocytosis usually signifies intercurrent infection such as pneumonitis, bacterial endocarditis, or pyelonephritis Moderate thrombocytopenia

and hypochromic anemia are regularly present The sedimentation rate is characteristically elevated and is apt to reach extreme levels in acute cases. The Wassermann and Kahn reactions give falsely positive results in a large minority of cases Indeed these reactions are sometimes positive long before the advent of any clinical evidences of S L E Hypoalbuminemia and marked hypergammaglobulinemia are characteristic Transfusion reactions are common These and other peculiarities of the blood (including the highly specific L E test) are described in detail elsewhere in the present symposium (25)

Cardiovascular System

A variety of troubles may beset the heart of the patient with S L E Inevitably the fever is accompanied by simple tachycardia, but at times the heart rate is rapid even when the temperature is little elevated Cardiac failure is unusual but may occur as a by-product of steroid treatment The pleural effusions which so frequently supervene are due to inherent disease of the serosa and not to passive congestion Myocarditis and pericarditis occur, the latter *being the commoner The pericarditis of lupus presents the usual clinical phe*nomena, substernal pain, dyspnoea, a tendency to sit with the trunk bent forward, and the usual physical and electrocardiographic signs Suppuration and calcification do not occur

A blowing apical systolic murmur occurs in many cases of S L E Careful retrospective studies have shown that this murmur cannot be correlated with the presence of non-bacterial verrucous endocarditis, i e with the cases which were formerly segregated under the designation of Libman-Sacks syndrome but which are now known to belong under the rubric of S L E (26) The murmurs and lesions of rheumatic heart disease are not rare in cases of S L E, but this appears to be nothing more than a confusing coincidence

In a small number of cases S L E is complicated by acute or subacute bacterial endocarditis Such patients run a fulminating course, with swinging "septic" fever, petechiae, splenomegaly, infarction of viscera, and positive blood culture With the advent of antibiotics and steroids such cases, never very common, are presumably becoming rare

The blood pressure in S L E is usually normal unless such complications as pericardial effusion or uremia are present Raynaud phenomena may occur during acute S L E or may have been among the patient's previous illnesses long before the emergence of the S L E syndrome

Lungs

The lungs are frequently involved in S L E Often the picture is that of persistent or migratory, patchy lobular pneumonia, usually accompanied by pleuritis and effusion Ordinarily the pleuritic signs and symptoms predominate over the pulmonary but this rule has been broken in several reported cases (27)

Dyspnea is extremely common The lungs may present wide-spread consolidation or focal infiltrative lesions, and the physical signs vary accordingly Commonly the lesions discovered at autopsy are more extensive than the physical

signs had indicated Roentgen films not infrequently reveal mottled and streaked shadows interpreted as subpleural infiltrates accompanied by areas of atelectasis. The pleurae may show local thickening and small or large effusions Ordinarily involvement is greatest at the bases Roentgenologists have learned to suspect the presence of S L E where pleural and subpleural lesions are present simultaneously (28). Before the advent of steroids the pneumonic lesions of S L.E. were tenacious and migratory. When pulmonic infiltrates are discovered in a case of S.L E. it is extremely and obviously important to exclude tuberculosis as the cause, occasionally the clinical and roentgen appearances have been indecisive. Ordinary bacterial pneumonia may occur in S L E. as in other chronic diseases.

Gastrointestinal Tract, Liver

Little is known about the behavior of the gastrointestinal tract in S L E. It is usual for lupus patients to have nondescript abdominal pain; a good many have intermittent diarrhea In some instances the pain is almost certainly due to lesions of the peritoneum, in others the intestinal vasculature is probably culpable Infarction may occur, and the use of steroids has brought with it occasional instances of perforation Usually abdominal and gastrointestinal symptoms in S.L E. are overshadowed by other troubles. Harvey, et al., have described ulcerative and diphtheritic esophagitis in lupus (21)

Hepatic symptoms are not prominent Moderate degrees of hepatomegaly are common, jaundice is rare Tests for hepatic function are apt to be vitiated by the hyperglobulinemia which is characteristic of the disease, hence the physician must use his own naked judgment Persistent pain and tenderness in the hepatic region are more suggestive of periarteritis nodosa than of S.L.E.

Kidneys

The kidneys are frequently attacked by the morbid process Most patients show at least albuminuria and microscopic hematuria. Alternatively the syndromes of acute nephritis or nephrosis present themselves In severe cases renal function suffers major damage, which leads to typical uremia and death As in any serious constitutional disease, pyelonephritis may appear, an unwelcome addition to the burden of the patient and the physician. The ocular changes which may accompany renal disease are discussed below.

The renal component of S L E. is of major importance because it is refractory to treatment, even by steroids, and because it is a principal immediate cause of death

Nervous System

A variety of neural and psychic disturbances may occur in S.L E. The commonest are epileptiform convulsions, delirium, and psychotic states, especially schizoid reactions and mania The ingenious discovery of the L E. test has made it possible to recognize S.L E as the underlying ailment in occasional persons who appeared to have ordinary idiopathic epilepsy. It is probable that

conscientious surveys of epileptic and schizophrenic patients will disclose small numbers of additional cases It is also not unusual for convulsions to occur in patients with S L E under treatment with steroids Such cases understandably confuse the physician, who may be at a loss to decide whether the convulsions are caused by the disease or the drug. At the present time opinion inclines toward continuing the steroid treatment, especially if the brain is not the only organ affected by the disease, but anticonvulsant drugs must often be added to the regimen

Other neural disturbances observed in S.L E. include peripheral neuritis (29), infarction of the spinal cord (30), and meningitis, especially the tuberculous variety

Eyes

The commonest ophthalmoscopic findings in S L E are hemorrhages and the so-called cotton-wool exudates The hemorrhages tend to occur around the retinal vessels and to be flame-shaped Hemorrhages in the vitreous humor have been reported Cotton-wool exudates are well defined, fluffy, yellowish-white deposits situated usually in the posterior half of the fundus Cyclical changes in these lesions have been reported (31) Cotton-wool exudates may occur independently of uremia, they are apt to appear in lupus patients who have cerebral signs Papilledema occurs in S L E but is rare, peripapillary edema is common.

Special Problems

S L E may occur coincidentally with many other diseases In some instances the apparent coincidence is merely a matter of erroneous diagnosis, in others the difficulty proceeds from our present inability to define the concept of S L E with satisfactory precision Thus, as has been stated in a previous paragraph, in cases where S L E appears to be coincidental with rheumatoid arthritis, the problem may be impossible to resolve The difficulty is almost as great in cases of rheumatic fever Indeed the case of a young negress has been reported in which Sydenham's chorea was followed within six weeks by S L E Autopsy revealed lesions of both diseases (32) Other ailments which have been reported to accompany S L E are neoplasms, Sjogren's syndrome (33), meningitis, and tuberculosis The latter is a constant but not insuperable danger during steroid treatment As previously stated, S L.E may be complicated by bacterial endocarditis and also by visceral or peripheral thrombosis and embolism, otitis media, abscesses of the skin, and parotitis

It has been demonstrated that sufferers from S L E may undergo major and minor surgical operations safely (34) Splenectomy has often been performed without immediate ill effect Post-operative problems in S L E are as likely to be caused by the steroids as by the basic disease

Much has been written about pregnancy in cases of S.L E but most of the information available dates from the pre-steroid era In a few cases the skin lesions disappeared during pregnancy but reappeared after parturition (35).

It is the general opinion that in most cases acute S.L.E. is affected favorably by pregnancy but that the risk of fetal death is high. Most authors regard abortion as unwarranted

DIAGNOSIS

The diagnosis of S.L.E. is beset with numerous difficulties. These have been alleviated but not dispelled by the discovery of the L.E. test, which is discussed elsewhere in the present symposium

As in so many other areas of clinical medicine, the first diagnostic act should be *to suspect*. A large variety of circumstances should lead the physician to think of S.L.E. These include (a) thrombopenic purpura or hemolytic anemia not attributable to drugs or poisons, (b) biologic false positive reaction for syphilis, (c) *continued fever of unknown origin; (d) arthralgia, especially when accompanied* by fever, pleuritis, pericarditis, pneumonia, cutaneous eruptions, or abnormal urine, (e) persistent or otherwise exceptional cases of pneumonitis. It would be well to add to this list cases of rheumatoid arthritis, dermatomyositis, scleroderma, idiopathic epilepsy, and schizophrenia. All these suspicions are fortified if the patient is a young woman or has recently been exposed to actinic radiation or has been given injections of gold salts. Suspicion should also attach to persons who have sunburn which has failed to clear in the usual time. Any unexplained deviations in persons who have discoid lupus should of course be subjected to careful study

The L.E. test, properly performed, rarely yields a false positive result. Such conditions as pernicious anemia, dermatitis herpetiformis, myeloma, and tuberculosis have been reported in this connection but not all such instances can be accepted unreservedly (36). The principal difficulty is provided by cases of hydralazine toxicity, since in these the patient may have fever, abdominal pain, polyserositis with effusion, pneumonitis, arthritis, and even a cutaneous eruption and hyperglobulinemia. "Hydralazine disease" astonishes rather than perplexes the clinician, since the use of the drug can usually be recognized; moreover hypertension is not characteristic of S.L.E. Another source of trouble is the patient to whom steroids have been given or are being given without a definite diagnosis. It is now well known that the use of steroids makes L.E. cells *hard to* find, indeed some physicians maintain that L.E. cells disappear during steroid treatment. In such cases diagnosis may be difficult or impossible unless the use of steroids can be interrupted.

There are also untreated cases of S.L.E. in which lupus cells are few or appear intermittently. In such cases the hyperglobulinemia and the abnormal urine may provide sufficient clarification until a positive test can be obtained

Biopsy of the skin, muscles, and kidney possesses only moderate reliability. Apart from the obvious facts that the procedure is no more reliable than the pathologist who executes it, and that not all pathologists can be depended upon to recognize the histologic picture, the microscopic changes of S.L.E. are difficult to detect. These changes are discussed authoritatively in another part of the present symposium. Biopsy is helpful—not invariably—in cases where the diag-

noses of scleroderma, periarteritis, and sarcoid must be excluded. Microscopical examination of spleens excised in cases of thrombopenic purpura or hemolytic anemia occasionally yields definite evidence of S.L.E.; hematoxylin bodies, "onion-skin lesions" (periarterial fibrosis) and peri-splenitis should be looked for diligently.

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SYSTEMIC LUPUS ERYTHEMATOSUS IN CHILDHOOD

DONALD GRIBETZ, M.D.

AND

WALTER L. HENLEY, M.D.

New York, N. Y.

INTRODUCTION

The incidence of systemic lupus erythematosus (S.L.E.) in children under the age of fifteen years is difficult to assess. Descriptions of large series of cases of this syndrome in adults indicate an incidence of approximately four to ten per cent in children in this age group (1, 2). Individual case reports are few (3-9), a group of eleven children, however, has been described (10). During the years between 1947 and 1958, fifteen patients with an onset of S.L.E. prior to the age of fifteen years were studied at The Mount Sinai Hospital.

The purpose of this report is to describe the syndrome as it appears in this age group and to discuss its course, prognosis and treatment. Differences, if any, between the syndrome in these children and in adults will be examined and features important to its differential diagnosis will be emphasized.

The discovery of the L.E. cell phenomenon (11) and the refinement of its use as a diagnostic technique have facilitated the recognition of this syndrome (12-15). The availability of antimicrobial drugs and hormonal agents has apparently prolonged the life of some patients with this disease. Accordingly, a greater familiarity with the clinical spectrum of S.L.E. as it pertains to children is essential to pediatricians.

CLINICAL MATERIAL

The fifteen cases of S.L.E. reviewed in this report include fourteen females and one male. The age of onset varied from five to fifteen years. All children were of the white race. Nine were Jewish and four were of Puerto Rican descent, this being a reflection of the patient population at The Mount Sinai Hospital.

Two patients were sisters who contracted the disease within two and one-half years of each other. Diagnosis in every case was not accepted until several positive L.E. cell preparations were obtained. Table I lists the essential findings in each patient.

CLINICAL FEATURES

The initial sign or symptom of these children is tabulated in Table II. The most frequent complaints included arthralgia, both with and without objective findings, rash, and fever. These symptoms are all similar to those of other "collagen" diseases. Four of the children had early symptoms not at all suggestive of this syndrome. These included menorrhagia, convulsions and edema. It is also of significance that a rash was present initially in only three of the patients.

From the Department of Pediatrics, The Mount Sinai Hospital, New York, N. Y.

TABLE I

Clinical Data of 15 Children with Systemic Lupus Erythematosus

Case No	Age at Onset (Yrs)	Sex	Initial Symptom	Major Early Signs & Symptoms: Arthralgia	Fever	Rash	Weight loss	Weakness	Pallor	Chest pain	Lid edema	Major Systems Involved: Reticulo-endothelial	Renal	Cardiac	C N S.	Hematopoietic	Pulmonary	Duration of Follow-Up (Yrs)	Present Status
1	5	F	Convulsions	+	+				+			LSN			+			1⅓	Remission
2	8	F	Pallor		+	+			+			LSN	+	+	+	+	+	2½	Dead
3	8½	F	Fever	+	+		+	+	+		+	N	+	+	+	+	+	3½	Dead
4	9¾	F	Fever		+	+							+					2½	Remission
5	10	F	Arthralgia	+	+		+					N	+	+				5	Remission
6	10	F	Rash	+	+	+			+			LSN	+	+	+			8½	Incomplete remission
7	10½	F	Rash	+	+	+	+		+			N	+	+				2	Dead
8	10½	F	Arthralgia	+	+		+	+										¾	Remission
9	10¾	M	Arthralgia	+	+	+						LS						¼	Remission
10	11½	F	Arthralgia	+		+	+					N	+	+	+	+		2¾	Dead
11	12	F	Edema	+		+	+	+		+	+	N	+	+			+	2½	Dead
12	12	F	Rash	+	+	+	+	+				LN	+	+	+		+	2	Dead
13	14	F	Menorrhagia	+						+		S		+		+		⅓	Remission
14	15	F	Arthralgia	+	+	+	+	+				L						1½	Remission
15	15	F	Arthralgia	+		+							+					1	?

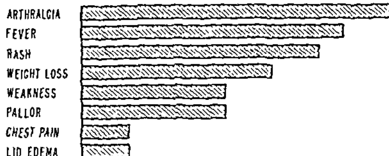
TABLE II

Initial Sign or Symptom in 15 Children with Systemic Lupus Erythematosus

Sign or Symptom	No of Children
Arthralgia	6
Rash	3
Fever	2
Pallor	1
Menorrhagia	1
Convulsions	1
Edema	1

Figure 1 is a graphic summary of the various signs and symptoms seen during the early stages of the disease It also depicts the frequency of major organ systems eventually involved during its course.

The most common sign, both at onset and during the progression of the disease, was joint involvement The joint symptoms were usually acute. Pain with or without local swelling and redness, was the chief manifestation. There was no predilection for specific joints, the interphalangeal joints being involved as frequently as knee, hip and elbow joints. Back pain occurred in two children and this was assumed to be due to intervertebral joint involvement Character-



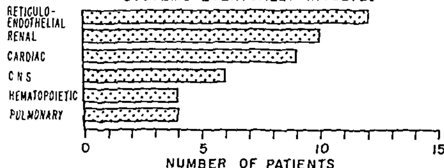


Fig 1

istic of the arthralgia, however, was the rarity of development of any permanent deformity regardless of the severity or the duration of the disease This may serve to differentiate this joint involvement from that of rheumatoid arthritis. Only one patient developed such a deformity One patient, interestingly, developed a transient nodule on the dorsum of a wrist

The fever pattern in these children was variable It varied from daily low-grade levels of 101° F to daily spikes of 103° to 104° F The fever was intermittent with recurrences usually heralding an exacerbation of the disease In no child did it spike to 105° or 106° F, as may be seen in rheumatoid arthritis.

Although the cutaneous manifestations of S L E were present in only three children as an initial sign, they appeared sometime during the course of the illness in two-thirds of the patients In the majority, there was the typical "butterfly" sunlight sensitive eruption involving the face. In two of the children a generalized non-specific maculo-papular eruption occurred on the trunk and extremities Three patients had oral lesions, two demonstrated vesicles and ulcers resembling herpetic stomatitis, one had ulcerated lesions secondary to hemorrhage into the mucous membrane

An outstanding sign which occurred early in more than one-half of the patients

was weight loss. It usually was accompanied by prominent anorexia. Weakness and pallor were also frequent in these children. Chest pain occurred in two patients as did "puffy" eyelids.

Although perhaps not present at the onset, several major systems became involved as the syndrome progressed. The "reticulo-endothelial system" was implicated in eighty per cent of the children. The majority had generalized lymphadenopathy either at the onset or during the course of the disease. One-third had hepatomegaly or splenomegaly, usually not at the onset. Only one child had clinical icterus

Two-thirds of the children have had renal involvement. This figure is probably closer to one hundred per cent since none of the five children who, thus far, are free of renal findings have been followed for more than one and a half years. Several children had albuminuria early in the course of the disease. Two had edema, either periorbital or ankle, at the onset. Seven of the ten children who have been followed for more than one and a half years have thus far developed a typical nephrotic syndrome In all who died, chronic renal disease was a contributing cause of death

Cardiac manifestations varied from a persistent systolic murmur as an isolated sign to such findings as ECG changes indicative of myocardial damage, hypertension and pericardial friction rubs In five of six fatal cases cardiac findings progressed to advanced myocardial involvement which in turn led to heart failure as a contributing factor in the deaths.

Six children had central nervous system manifestations These included grand mal seizures at the onset of the disease in two children, blurred vision in two, ankle clonus in one child and an abnormal EEG in the sixth /

Four of the children have thus far had hemorrhagic tendencies. One presented with menorrhagia as the initial symptom of the disease The other three had bleeding episodes involving the nose, oral cavity and skin

Table III is a listing of other diagnoses considered in these children prior to the confirmation of S L E A perusal of these conditions associated with the previous discussion of the diverse signs and symptoms is a testament to the protean and frequently confusing picture presented during the early months of this illness In fact, review of the histories reveals a significant delay in time between the onset of symptoms and definitive diagnosis. In only three children was the diagnosis made during the initial contact The diagnosis was made in seven children within six months after initial examination but it was delayed from one to three and a half years in five. The average duration of "lag" was

TABLE III

Other Diagnoses Considered in 15 Children with Systemic Lupus Erythematosus

Acute glomerulonephritis	Infectious mononucleosis
Acute hemolytic anemia	Rubella
Acute leukemia	Rheumatic fever
Allergic rash	Infectious arthritis
Epilepsy	Traumatic arthritis
"Viral" infection	

ten months. Several of the patients were treated for allergy, infection, traumatic or infectious arthritis and epilepsy prior to the eventual recognition of the underlying disease

LABORATORY FINDINGS

Except for the finding of the L E cell phenomenon, no individual laboratory test was of diagnostic significance The L E cell test as performed in our laboratory (16) was positive in all patients once the diagnosis was considered.

The majority of the children had a depression of their hemoglobin levels either at the onset or during the course of the disease As previously indicated, in only four could this have been due to actual blood loss Eight of twelve patients, in whom this test was performed, demonstrated a positive Coombs reaction *Platelet counts were depressed in approximately one-half of the patients*

All of the patients had a leukopenia varying from 3000 to 6000 cells per cu mm during the course of the disease, nearly all had a polymorphonuclear leukocytosis

The sedimentation rate was elevated in all of the patients, although in three it did not rise until several months had elapsed The Wassermann reaction was positive in only two of seven patients in whom it was performed The albumin/globulin ratio was reversed in one-half of the patients at the onset of the disease, even before kidney involvement was evident

Although albuminuria was present in nine of the patients at the onset, other laboratory signs of renal impairment such as the appearance of urinary formed elements, elevated blood urea nitrogen, elevated serum cholesterol and depressed clearance tests and PSP excretion did not appear until the disease had progressed

Gamma globulin elevation was noted in four of six patients in whom serum protein patterns were studied by electrophoresis, in two patients the level was below normal

COURSE AND PROGNOSIS

The present status of fourteen of the fifteen patients is known Only ten children have, thus far, been followed for more than one and a half years after onset, six have succumbed

The course of those who died was characterized by repeated exacerbation with additional systemic involvement and increased severity occurring with each recrudescence Death occurred, on the average, two to three years after onset and was due usually to a combination of cardiac and renal failure Three patients had autopsy examinations Pathologic features well described in adult series were found, i e , the typical "lupus nephritis" accompanied by endocarditis and myocarditis (17, 18) Of interest is the fact that three children are living in remission despite the fact that their disease began two and one-half, five and eight and one-half years ago

TREATMENT

Therapy in children does not differ from that employed in adults Supportive measures include an adequate diet with vitamins, anti-pyretics, transfusions,

digitalis and, especially, antibiotics. Steroids are reserved for periods of severe symptomatology not ameliorated by the above measures. The initial dosage should be large enough to control symptoms quickly, usually 200 to 300 mg. of cortisone or 40 to 60 mg of prednisone Efforts are then made to reduce the drug to a maintenance level sufficient to keep the signs and symptoms quiescent, usually 75 to 100 mg of cortisone or 15 to 20 mg. of prednisone daily Intermittent attempts to wean the patient from the steroid are also made; the drug is reinstituted when severe symptoms reappear. It is of interest that the nephrotic syndrome secondary to S.L E does not respond with either immediate diuresis or prolonged remission to steroids as does the idiopathic form of nephrotic syndrome of childhood.

Recently, analyses of large series of cases of S L.E. in adults, have led to a somewhat more optimistic outlook concerning the prognosis (19, 20). Harvey has stated that more than fifty per cent of ninety-nine patients have survived for four or more years (2) Although there have been no extensive follow-ups in children, the conclusion has generally been accepted that survival in this age group is shorter In the present series, three of the children survived from two and one-half to eight and one-half years after the onset of their symptoms It would appear therefore that appropriate therapy with antimicrobial drugs and hormonal agents may serve to ameliorate symptoms and prolong life

DISCUSSION

As has been discussed, the clinical manifestations of S L E are protean and the organ involvement is multiple. It should be emphasized that the diagnosis can be made in the early stages only if it is considered

The early presence of the typical "butterfly" eruption is the best clue to diagnosis Rashes of varying types however, have been described (21), in the present series the diagnoses of rubella, infectious mononucleosis and allergy were considered in three children Of importance is the observation that five children had no rash of any type during the course of their disease When, in addition to the three most common early symptoms (arthralgia, fever and rash), the disease has progressed to include renal involvement, hemorrhagic manifestations, or polyserositis, recognition presents no problem. Most important is its diagnosis during the early stages, during the period when intermittent arthralgia or recurring fever are the cardinal symptoms

Several clinical features gleaned from analysis of the fifteen children in this series may be of aid in establishing the early diagnosis of S L.E :

A The early accompaniment of arthralgia and fever by anorexia and weight loss,

B. The early appearance of generalized lymphadenopathy and/or hepatomegaly and splenomegaly,

C. Renal involvement as evidenced only by albuminuria or hematuria (the diagnosis of acute glomerulonephritis was entertained for several weeks on patient number 4 before S L E. was considered);

D Central nervous system signs, especially convulsions (patient number 1

presented with grand mal seizures and was considered to be an epileptic for one year prior to the appearance of other manifestations),

E Hemolytic anemia

Although, as has been pointed out, none of the routine laboratory tests are specific, the coexistence of an elevated sedimentation rate, leukopenia with polymorphonuclear leukocytosis and an elevated serum globulin level would be highly suggestive A positive Coombs test and/or a positive serologic test for syphilis may also be found As has been stressed by many workers only the repeated performance of the L E cell test in all patients presenting any of the suggestive signs and symptoms will ferret out cases in the early stages of the disease (19, 22)

SUMMARY

A group of fifteen children with S L E beginning prior to the age of fifteen years is described Early signs and symptoms, subsequent visceral involvement, laboratory findings, course, treatment, and outcome are analyzed Features pertinent to the early differential diagnosis are emphasized

It appears that the clinical picture in this age group does not differ markedly from that described in adults It also is evident that the course and prognosis in the two age groups are similar It is concluded that an early diagnosis of this syndrome can be established by greater awareness of the varied clinical picture and with the more frequent performance of L E cell preparations

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THE THERAPY OF SYSTEMIC LUPUS ERYTHEMATOSUS

LOUIS J SOFFER, M.D

New York, N. Y.

The advent of corticotropin and the adrenal glucogenic steroids constituted the first significant advance in the therapeutic management of systemic lupus erythematosus (1, 2). During the course of the decade that these agents have now been employed, they have proven to be quite effective in the control of most of the clinical mainfestations of this illness (3-9) This is somewhat less true of other collagen diseases such as polyarteritis nodosa and dermatomyositis, while their ability to subdue the progression of scleroderma is at best meager

Systemic lupus erythematosus is a disease of protean complexity but is often characterized by fever, joint pains, rash, lymphadenopathy, involvement of the serous cavities, hepatomegaly, splenomegaly, various blood dyscrasias, and impaired renal function. In Tables I and II are listed the symptoms and physical signs that we encountered in our group of fifty-five patients with lupus, while in Table III are recorded the laboratory data obtained in these patients With the exception of the impairment of renal function, most of the other manifestations are promptly brought under control with either corticotropin or the adrenal steroids Following administration of the hormone in adequate amounts, the temperature usually returns to normal levels within twelve to thirty-six hours, the arthralgias and arthritis subside appreciably within one or two days, while the rash disappears almost entirely, except for a faint brown scaliness, within a week. Pleural and pericardial collections of fluid are absorbed, the latter somewhat less rapidly than the former (Table IV) The enlarged liver, when not due to congestive heart failure, seldom returns to normal but generally does become somewhat reduced in size Essentially the same is true for the splenomegaly A previously false positive serology becomes negative in twenty to thirty per cent of those patients whose serology was previously positive

In no instance in our group have the L. E. cells entirely disappeared from the peripheral blood Their abundance is significantly decreased when the disease is brought under control, but we have never failed to find them with patient and careful search Thrombocytopenia and hemolytic anemia occurring during the course of the illness respond most satisfactorily to treatment with the hormonal agents Indeed, the response to treatment of the latter manifestation, which in the past represented such a dire hazard to the patient with systemic lupus erythematosus, is most dramatic in the promptness of remission It is interesting to observe, however, that although the hemolytic phenomena cease, the positive Coombs' test remains unaltered (Table V) In patients with thrombocytopenia, the blood platelets rapidly increase in number, and purpura, when present, subsides

From the Department of Medicine, The Mount Sinai Hospital, New York N. Y.

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TABLE I

Incidence of Symptoms in 55 Patients with Acute Systemic Lupus Erythematosus

Symptom	Patients	
	Number	Per cent
Arthralgia	52	95
Fever	50	91
Weight loss	36	65
Rash	34	62
Arthritis	34	62
Chest pain	20	36
Chills or chilliness	17	31
Abdominal pain	11	20
Convulsions	11	20
Alopecia	10	18
Lymphadenopathy	9	16
Light sensitivity	6	11
Bleeding tendency	6	11
Paresthesia	1	2

TABLE II

Incidence of Physical Signs in 55 Patients with Acute Systemic Lupus Erythematosus

Physical Sign	Patient	
	Number	Per cent
Lymphadenopathy	39	71
Rash	34	62
Mucous membrane lesions	19	35
Joint abnormalities	28	51
Hepatomegaly	26	47
Cardiac abnormalities (total)	20	36
Hypertension	7	13
Significant murmur	6	11
Gallop rhythm	5	9
Pericardial friction rub	4	7
Pericardial effusion	4	7
Pulmonary abnormalities (total)	18	33
Pleural effusion	7	13
Friction rub	6	11
Splenomegaly	14	25
Psychiatric abnormalities	13	24
Edema	12	22
Finger-tip skin lesions	9	16
Fundal abnormalities	9	16
Petechiae	6	11
Neurological abnormalities	5	9

TABLE III

Laboratory Data in 55 Patients with Acute Systemic Lupus Erythematosus

	Patients	
	Number	Per cent
Positive L.E. test	55	100
Elevated sedimentation rate	51	93
Hyperglobulinemia	39	71
Cephalin flocculation test (2+ to 4+)*	30	68
WBC less than 5000/cu mm	35	64
Urine		
Sediment, occasional to many WBC	32	58
Sediment, occasional to many RBC	22	40
Sediment, occasional to many casts	14	25
Albumin, 1+ or more	27	49
Hemoglobin less than 10 gm /100 cc	29	53
Abnormal EEG**	8	50
Abnormal chest x ray	20	36
Azotemia	17	31
Creatinine greater than 1.5 mg /100 cc †	12	41
False positive serologic test for syphilis	15	27
Abnormal ECG	12	22
Prolonged bleeding time‡	4	22
Platelets less than 100,000/cu mm	9	16
C reactive protein test, 1 or more††	8	67
Differential sheep cell agglutinin test, titer greater than 1:16§	1	14

* 44 patients
** 16 patients
† 29 patients
‡ 18 patients
†† 12 patients
§ 7 patients

In our group, the sedimentation rate returned to normal levels in over half of the cases. The persistence of an elevated sedimentation rate was usually associated with inadequate treatment, the presence of significant impairment of renal function, or the existence of some underlying complication or infection. Similarly, reduction in the preexisting hyperglobulinemia occurred in only slightly more than half of the patients. Patients with systemic lupus erythematosus almost always develop a normochromic anemia of varying intensity. The anemia responds slowly to steroid or corticotropin therapy. The hemoglobin and peripheral red blood cell count returned to normal levels in approximately half of our group. Most of our patients, however, did show an increase in the peripheral white blood cell count with a return of the presence of more mature granulocytes.

The major continuing threat to life of patients with systemic lupus erythema-

TABLE IV

Effect of Treatment on the Clinical Manifestations of Acute Systemic Lupus Erythematosus

Clinical Manifestation	Total No. of Patients	Total Improved (per cent)
Fever	47	100
Arthralgia	50	100
Weight loss	35	66
Lymphadenopathy	36	56
Rash	32	91
Mucous membrane lesions	19	74
Hepatomegaly	25	20
Cardiac abnormalities	20	35
Hypertension	7	0
Gallop rhythm	5	60
Pericardial friction rub	4	50
Pericardial effusion	4	50
Significant murmur	6	0
Pulmonary abnormalities	18	94
Pleural friction rub	6	100
Pleural effusion	7	71
Chest pain	20	90
Psychiatric abnormalities	13	62
Finger tip skin lesions	9	44
Abdominal pain	11	73
Edema	12	58
Splenomegaly	14	14
Alopecia	9	44
Fundal abnormalities	9	67
Neurological abnormalities	5	20

tosus, despite adequate steroid therapy, is the development of persistent and progressive renal disease Approximately half our patients showed some renal function abnormalities, as evidenced by the presence of red blood cells in the urinary sediment and varying degrees of albuminuria In slightly over one-third of the group the blood urea nitrogen was elevated (Table III). Renal function studies, such as urine concentration tests, phenolsulphonthalein excretion, and urea and creatinine clearance, were determined in slightly more than half of the patients These studies revealed several points of interest. The urine concentration test proved to be the least sensitive indicator of the status of renal function as observed in this group On the other hand, the fifteen-minute excretion of phenolsulphonphthalein and the urea clearance yielded the most useful information in terms of appraisal of the renal status

Renal involvement in systemic lupus is the least responsive of all the clinical manifestations of the disease to the adrenal glucogenic steroids or corticotropin. Of fifty-five patients studied in our clinic between 1948 and 1955, seventeen died Of these, thirteen succumbed to progressive renal failure despite intensive and prolonged therapy The nephrotic syndrome often encountered in this illness

TABLE V

Effect of Treatment on the Laboratory Data in Acute Systemic Lupus Erythematosus

Laboratory Test	Number of Patients Before Therapy	Percentage of Patients Improved
Positive L E test	55	0
Elevated ESR	49	57
Hyperglobulinemia	37	46
WBC less than 500/cu mm	32	72
Hemoglobin less than 10 gm /100 cc	28	54
Urine		
Sediment, occasional to many RBC	22	32
Sediment, occasional to many WBC	32	50
Sediment, occasional to many casts	14	36
Albumin, 1 plus or more	27	26
Abnormal chest x ray	20	60
False positive serologic test for syphilis	14	29
Azotemia	17	35
Shift to left (nonsegmented forms greater than 10%	32	41
Abnormal EEG	8	0
Reticulocytes greater than 0 7%	19	37
Cephalin flocculation greater than 1 plus	29	14
Abnormal electrocardiogram	12	42
Prolonged bleeding time	4	75
C reactive protein test greater than 1 plus	8	25
Platelets less than 100,000	8	63
Positive direct Coombs' test	8	0
Hemolysis	4	100

may show a gratifying temporary response to salt and fluid restriction and hormone therapy But, unfortunately, the underlying renal disease progresses inexorably

During an acute relapse of the illness, when the temperature is considerably elevated, albuminuria, the presence of cellular elements in the urine, and an elevation of the blood urea nitrogen are not infrequently found With the subsidence of the acute disease process, the abnormal urinary constituents will often disappear and the blood urea nitrogen value will return to normal levels Whether this represents actual renal disease, characteristic of systemic lupus erythematosus, or is a manifestation of the general toxicity associated with the acute exacerbation of the illness, is uncertain In any event, evidence of persistent and significant impairment in renal function was almost invariably encountered in those individuals who succumbed to the disease It is our opinion that the renal status, after prolonged and adequate therapy, is the single most important factor in determining the prognosis of the individual patient Evidence of persistent or progressive impairment of kidney function must, in general, be regarded as an ominous sign

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TABLE VI

Comparative Effects of Adrenal Steroids on Sodium Retention, Potassium Diuresis, Protein and Carbohydrate Metabolism (16)

Hormonal Agent	Sodium Retaining Effect	Potassium-Diuretic Effect	Effect on Protein and Carbohydrate Metabolism
Cortisone	1	1	1
Cortisol	1 25	1	1 25
Prednisone	none	slight	3–5
Prednisolone	none	slight	3–5
6 Methylprednisolone	none	slight	4–6
2 Methylcortisol	80–100	5–10	4–5
Desoxycorticosterone acetate	30–50	5	0
Aldosterone	300–900	10–25	0
9α Fluorocortisol	300–900	10–25	10–15
9α Fluoroprednisolone	300–900	10–25	50
2 Methyl-9α-fluorocortisol	1000–2000	?	9
9α Fluoro-16 hydroxyprednisolone (triamcinolone)	none	?	4–6

who have impairment of renal function generally manifest this early in the course of the illness (10) The longer the disease remains established without development of this complication, the less likely is it to occur.

*The treatment of systemic lupus erythematosus consists of vigorous admin*istration of hormone and, where cortisone, cortisol, or corticotropin is employed rigid restriction of the daily salt intake. Such sodium restriction is much less necessary when certain of the newer adrenal steroid analogues are used (Table VI) When prolonged steroid therapy is contemplated, it is essential that the patient receive daily supplemental potassium. Two to three grams of potassium chloride a day is usually adequate to prevent development of hypokalemia. The newer steroids, such as prednisone, prednisolone, *6*-methyl prednisolone (Medrol®), and perhaps some of the even more recent analogues, tend less to induce a potassium diuresis than do corticotropin, cortisone, and cortisol (11, 12).

The acute toxic manifestations of the disease are promptly brought under control when an *adequate* amount of hormone is administered. In Table VII are listed the usual initial and maintenance doses of the various steroids, with which we have had experience, required to return the elevated temperature to normal levels and suppress the toxic manifestations.

It should be emphasized that the therapeutic hormonal requirements of the individual patient may vary considerably from the mean Where the acute exacerbation does not respond promptly to the usual initial dosage there should be no hesitancy in increasing it to whatever level is necessary to induce an adequate remission

When corticotropin is employed, several alternative routes and agents are available (a) aqueous corticotropin administered intramuscularly, in a dosage of twenty-five to fifty units every six hours around the clock, (b) intravenously in a dosage of twenty to forty units administered in a continuous intravenous

TABLE VII

Comparative Effectiveness of the Adrenal Steroids as Anti Inflammatory Agents in Man (16)

Hormonal Agent	Anti-Inflammatory Activity	Average Initial Daily Oral Dose (mg)	Average Daily Oral Maintenance Dose (mg)
Cortisone	1	200-300	50-100
Cortisol	1-1.25	200-300	50-100
Prednisone	3-5	40-60	10-25
Prednisolone	3-5	40-60	10-25
6 Methylprednisolone	3-5	32-48	8-24
3 Methylcortisol	4-5	30-50	5-20
Desoxycorticosterone acetate	0	—	—
Aldosterone	0-[illegible]	—	—
9α-Fluorocortisol	10-15	8-12	4-6
9α-Fluoro-16-hydroxyprednisolone	3-5	32-48	8-24

infusion of five per cent glucose over an eight hour period daily, (c) zinc corticotropin, twenty to forty units twice a day intramuscularly. Of these measures the intramuscular zinc corticotropin and the intravenously administered corticotropin are perhaps most promptly effective. When the acute manifestations of the disease have been brought under control, both zinc and gel corticotropin may be used for maintenance purposes, the former in a dosage of ten to forty units daily, the latter in somewhat larger amounts.

With the introduction of atabrine in the treatment of discoid lupus (13) the value of the antimalarial agents were explored in the management of systemic lupus erythematosus (14, 15). In a recent report, Dubois describes equally good results with both atabrine and chloroquin (15). Twelve of fourteen patients in this group were benefited. Our experience with chloroquin has been less satisfactory in terms of control of the toxic manifestations of the disease. The latter often respond poorly, and in the presence of severe manifestations generally not at all. On the other hand, the rash, when present, subsides within several days after beginning chloroquin therapy. The use of these agents is not without hazard, since leukopenia, exfoliative dermatitis, and gastrointestinal disturbances have followed upon their administration (15). The dosage of chloroquin generally employed varies from 250 to 500 mg daily. The use of chloroquin as an adjuvant to treatment with steroids has failed in our experience to demonstrate any overt advantages over the use of the steroids alone.

Although the glucogenic corticoids are effective in the suppression of many of the manifestations of systemic lupus erythematosus, the development of certain side effects consequent to their use must be borne in mind. Perhaps the term "side effects" is a misnomer, since such effects may represent specific metabolic actions of these agents. In any event, the efforts of the organic chemist are now being extensively directed to the synthetic preparation of fractions with maintained or increased anti-inflammatory activity but devoid of those effects which we may consider undesirable for our purposes.

Our experience with the various glucogenic steroids which we have thus far employed in the treatment of this disease would indicate that, with the exception of their various effects on electrolyte and fluid metabolism, the other effects occur with approximately equal frequency. Prolonged administration of corticotropin or the adrenal fractions will result in the development of many of the manifestations of Cushing's syndrome. The severity of these manifestations will, of course, depend upon the amounts of hormone used and the duration of treatment. Edema is less likely to occur with prednisone, prednisolone or Medrol® than with other agents. These last three agents are generally not salt-retaining However, this complication can be almost entirely eliminated when corticotropin, cortisol, or cortisone is used, provided the daily sodium intake is restricted With control of this complication, congestive heart failure, previously so prone to occur in the hormonally treated patient with systemic lupus erythematosus, rarely develops. The incidence of hypertension as a complication of hormone treatment in patients with this illness is similarly lowered with reduction in the daily salt intake

Hyperglycemia and glycosuria are occasionally encountered This complication, however, has greater clinical significance in the diabetic than in the normal individual This is a reversible complication in the non-diabetic when the dosage of hormone is reduced or eliminated, and the insulin requirement in the diabetic patient becomes lowered under the same circumstances. Osteoporosis can be a more distressing hazard, but is of greater moment in the older age group In the patient with post-menopausal or senile osteoporosis, prolonged administration of the hormonal agents may result in collapse of the vertebrae and readily induced rib fractures The severity of this complication may to some extent be reduced by the concomitant administration of androgen to the male patient, and combined androgen and estrogen to the female.

Psychotic manifestations, the development of peptic ulcer, perforation of a duodenal or gastric ulcer already present, and the activation and dissemination of a semi-quiescent tuberculosis are not uncommon complications Dissemination of a fungus infection is, fortunately, less common It is interesting to observe, however, that when the patient with systemic lupus erythematosus develops a peptic ulcer while receiving steroid therapy, the continued administration of the hormone may not interfere with the normal healing process of the ulcer when he is placed upon a proper ulcer regimen. I am not sure, however, that the development of a peptic ulcer can be prevented by the prophylactic institution of an ulcer regimen The problem as to whether a patient with an ulcer history should be treated with steroids depends essentially upon the nature and severity of the underlying disease for which the use of the steroid is planned. In the instance of active systemic lupus erythematosus, the hazard of this illness is so considerable and its response to hormone therapy so gratifying, that even in the face of an existing peptic ulcer we have no choice but to submit the patient to whatever dangers are involved in the use of the steroids as being the lesser of the two evils I would assume that the same philosophy must apply in the presence of tuberculosis Here the problem is perhaps less acute in that the

available treatment for tuberculosis is effective and can prophylactically prevent either the activation or dissemination of a latent or quiescent form of the disease

A most important complication following prolonged use of corticotropin and the adrenal steroids is the development of a hypochloremic, hypokalemic alkalosis with its attendant cardiac arrhythmias and sudden cardiac accidents. This development is often a subtle one and not necessarily heralded by the prior advent of electrocardiographic changes or overt but innocent cardiac arrhythmias. Hypotassemia occurs as a result of the potassium diuresis which follows administration of corticotropin, cortisol, and cortisone. Prednisone, prednisolone, and Medrol® induce very little urinary potassium loss, and therefore this complication is much less likely to occur with these latter agents. To avoid this serious complication, it is desirable that all patients receiving corticotropin or the usual currently available adrenal glucogenic steroids for periods longer than ten days should routinely be given two to three grams of potassium chloride daily by mouth.

There are two additional complications following the use of steroids to be considered particularly in the management of this disease (a) convulsive episodes, and (b) development of muscular dystrophy involving the thigh and girdle muscles. Convulsions may occur either as a result of inadequate therapy or due to excessive therapy with unrestricted salt intake. Where such episodes occur early in the course of treatment and are not associated with other evidence of fluid retention, the probabilities are that they are due to the cerebral involvement of the disease process and call for more vigorous steroid therapy. It is interesting to note, however, that when we learned of the importance of restriction of salt intake when corticotropin, cortisol, or cortisone is used (9), or when we substituted the newer adrenal steroid analogues, the incidence of this complication fell appreciably.

Three of our fifty-five patients developed marked weakness of the thigh and hip muscles. In each of the three instances this complication occurred after more than one year of continuous treatment with cortisol or cortisone. The first evidence of this disability was the difficulty that the patient had in rising from a sitting position without help, and was associated with the appearance of ribose in the urine in one instance. This affliction was slow in development, but progressive and unresponsive to administration of androgens. Where treatment with steroids could be discontinued for adequate periods of time, some improvement followed. But when therapy was once more instituted, the disability almost always promptly reappeared.

In attempting to evaluate the overall results of therapy, it becomes evident that systemic lupus erythematosus is not cured with corticotropin or the currently available steroids. There are several manifestations of the illness which are not at all, or only minimally, affected by these measures. Most prominent of these, of course, is the lack of any appreciable influence on the development and progression of renal disease once it has occurred. This is unfortunate, since most of the deaths in this disease today occur as a result of progressive renal failure. On the other hand, many of the acute and chronic manifestations of

the illness are promptly brought under control and a significant percentage of the patients are satisfactorily rehabilitated, and with continuous or intermittent therapy are maintained in a reasonably good state of health. The complications directly related to treatment are indeed disconcerting. Their incidence, however, can be appreciably reduced by careful use of the hormonal agents and a constant awareness of the possibility of their occurrence. These agents, nevertheless, constitute a very significant advance and represent the most effective measures currently available for the management of this illness

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